Pyrazolo[3,4-b]pyridine compounds, and their use as phosphodiesterase inhibitors

The present invention relates to pyrazolopyridine compounds, processes for their preparation, intermediates usable in these processes, and pharmaceutical compositions containing the compounds. The invention also relates to the use of the pyrazolopyridine compounds in therapy, for example as inhibitors of phosphodiesterases (PDE) and/or for the treatment and/or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis or allergic rhinitis.

US 3,979,399, US 3,840,546, and US 3,966,746 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxamides wherein the 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 3-6-membered heterocyclic group such as pyrrolidino, piperidino and piperazino. The compounds are disclosed as central nervous system depressants useful as ataractic, analgesic and hypotensive agents.

US 3,925,388, US 3,856,799, US 3,833,594 and US 3,755,340 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxylic acids and esters. The 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 5-6-membered heterocyclic group in which an additional nitrogen is present such as pyrrolidino, piperidino, pyrazolyl, pyrimidinyl, pyridazinyl or piperazinyl. The compounds are mentioned as being central nervous system depressants useful as ataractic agents or tranquilisers, as having antiinflammatory and analgesic properties. The compounds are mentioned as increasing the intracellular concentration of adenosine-3',5'-cyclic monophosphate and for alleviating the symptoms of asthma.

H. Hoehn et al., *J. Heterocycl. Chem.*, 1972, 9(2), 235-253 discloses a series of 1*H*-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives with 4-hydroxy, 4-chloro, 4-alkoxy, 4-hydrazino, and 4-amino substituents.

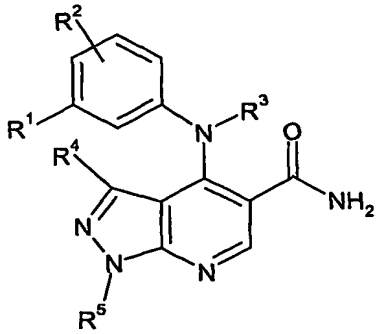
CA 1003419, CH 553 799 and T.Denzel, *Archiv der Pharmazie*, 1974, 307(3), 177-186 disclose 4,5-disubstituted 1*H*-pyrazolo[3,4-b]pyridines unsubstituted at the 1-position.

US 3,833,598 and GB 1,417,489 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-6-carboxylic acids and esters. The 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl, R_6,R_7-phenyl, etc.; or NR_3R_4 can be a 5-6-membered heterocyclic group in which an additional nitrogen is present, namely optionally substituted pyrrolidino, piperidino, pyrazolyl, dihydropyridazinyl or piperazinyl. At the 5-position of the pyrazolo[3,4-b]pyridine is group R_5 which is hydrogen, lower alkyl, phenyl, phenyl-lower-alkyl or

halogen; R_5 is preferably hydrogen, methyl or chlorine. The compounds are mentioned as being central nervous system depressants useful as tranquilizers or ataractic agents for the relief of anxiety and tension states. The compounds are also mentioned as increasing the intracellular concentration of adenosine-3',5'-cyclic monophosphate and for alleviating the symptoms of asthma. The compounds are also mentioned as having anti-inflammatory properties and as being useful as anti-inflammatory agents, for example, to reduce local inflammatory conditions such as those of an edematous nature or resulting from proliferation of connective tissue in various mammalian species such as rats and dogs.

US 4,115,394 and GB 1,511,006 (E.R.Squibb & Sons) disclose 4-amino derivatives of 6-phenyl-pyrazolo[3,4-b]pyridines. The 4-amino group NR_3R_4 is an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl, phenyl, phenyl-lower-alkyl or substituted phenyl. At the 5-position of the pyrazolo[3,4-b]pyridine is group R_5 which is hydrogen, lower alkyl, phenyl or phenyl-lower-alkyl; R_5 is preferably hydrogen. The compounds are mentioned as having anti-inflammatory properties and as being useful as anti-inflammatory agents, for example, to reduce local inflammatory conditions such as those of an edematous nature or resulting from proliferation of connective tissue in various mammalian species such as rats and dogs. The compounds are also mentioned (a) as having diuretic activity, and (b) as increasing the intracellular concentration of adenosine-3',5'-cyclic monophosphate and for alleviating the symptoms of asthma.

Japanese laid-open patent application JP-2002-20386-A (Ono Yakuhin Kogyo KK) published on 23 January 2002 discloses pyrazolopyridine compounds of the following formula:



JP-2002-20386-A
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wherein R^1 denotes 1) a group $-OR^6$, 2) a group $-SR^7$, 3) a C2-8 alkynyl group, 4) a nitro group, 5) a cyano group, 6) a C1-8 alkyl group substituted by a hydroxy group or a C1-8 alkoxy group, 7) a phenyl group, 8) a group $-C(O)R^8$, 9) a group $-SO_2NR^9R^{10}$, 10) a group $-NR^{11}SO_2R^{12}$, 11) a group $-NR^{13}C(O)R^{14}$ or 12) a group $-CH=NR^{15}$. R^6 and R^7 denote i) a hydrogen atom, ii) a C1-8 alkyl group, iii) a C1-8 alkyl group substituted by a C1-8 alkoxy group, iv) a trihalomethyl group, v) a C3-7 cycloalkyl group, vi) a C1-8 alkyl group substituted by a phenyl group or vii) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^2 denotes 1) a hydrogen atom or 2) a C1-8 alkoxy group. R^3 denotes 1) a hydrogen

atom or 2) a C1-8 alkyl group. R^4 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group, 5) a phenyl group which may be substituted by 1-3 halogen atoms or 6) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^5 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group or 5) a phenyl group which may be substituted by 1-3 substituents. In group R^3, a hydrogen atom is preferred. In group R^4 , methyl, ethyl, cyclopropyl, cyclobutyl or cyclopentyl are preferred. The compounds of JP-2002-20386-A are stated as having PDE4 inhibitory activity and as being useful in the prevention and/or treatment of inflammatory diseases and many other diseases.

EP 0 076 035 A1 (ICI Americas) discloses pyrazolo[3,4-b]pyridine derivatives as central nervous system depressants useful as tranquilisers or ataractic agents for the relief of anxiety and tension states.

The compound cartazolate, ethyl 1-ethyl-4-n-butylamino-1H-pyrazolo[3,4-b]-pyridine-5-carboxylate, is known. J.W. Daly et al., *Med. Chem. Res.*, 1994, 4, 293-306 and D. Shi et al., *Drug Development Research*, 1997, 42, 41-56 disclose a series of 4-(amino)substituted 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives, including ethyl 4-cyclopentylamino-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate, and their affinities and antagonist activities at A_1- and A_{2A}-adenosine receptors, and the latter paper discloses their affinities at various binding sites of the $GABA_A$-receptor channel. S. Schenone et al., *Bioorg. Med. Chem. Lett.*, 2001, 11, 2529-2531, and F. Bondavalli et al., *J. Med. Chem.*, 2002, vol. 45 (Issue 22, 24 October 2002, allegedly published on the Web on 09/24/2002), pp. 4875-4887, disclose a series of 4-amino-1-(2-chloro-2-phenylethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl esters as A1-adenosine receptor ligands.

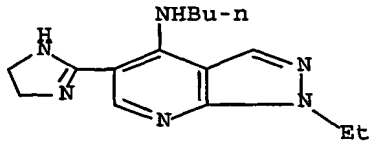
WO 02/060900 A2 appears to disclose, as MCP-1 antagonists for treatment of allergic, inflammatory or autoimmune disorders or diseases, a series of bicyclic heterocyclic compounds with a $-C(O)-NR^4-C(O)-NR^5R^6$ substituent, including isoxazolo[5,4-b]pyridines and 1*H*-pyrazolo[3,4-b]pyridines (named as pyrazolo[5,4-b]pyridines) with the $-C(O)-NR^4-C(O)-NR^5R^6$ group as the 5-substituent and optionally substituted at the 1-, 3-, 4-, and/or 6-positions. Bicyclic heterocyclic compounds with a $-C(O)NH_2$ substituent instead of the $-C(O)-NR^4-C(O)-NR^5R^6$ substituent are alleged to be disclosed in WO 02/060900 as intermediates in the synthesis of the $-C(O)-NR^4-C(O)-NR^5R^6$ substituted compounds.

S.S.Chakravorti et al., *Indian J. Chem.*, 1978, 16B(2), 161-3 discloses the compounds 4-hydroxy-1,3-diphenyl-5-(3',4'-dihydroisoquinol-1'-yl)-pyrazolo[3,4-b]pyridine and 1,3-diphenyl-4-hydroxy-5-(3'-methyl-3',4'-dihydroisoquinol-1'-yl)-

pyrazolo[3,4-b]pyridine. These two compounds were tested for antifilarial activity but were found to have no significant microfilaricidal activity.

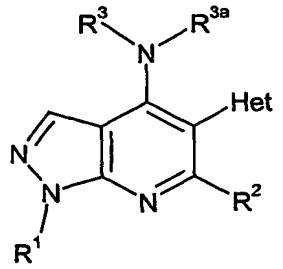
G. Sabitha et al., *Synthetic Commun.*, 1999, 29(4), 655-665 discloses a synthetic route to 5-substituted-6-amino-1-phenyl-3-(methyl or phenyl)-pyrazolo[3,4-b]pyridines wherein the 5-substituent of the pyrazolo[3,4-b]pyridine is benzimidazol-2-yl, 5-chloro-benzoxazol-2-yl, or benzothiazol-2-yl. Though declared to be "biologically interesting molecules", there is however no disclosure that these compounds had been tested in any pharmacological tests and there is no disclosure of any general or specific biological activity of these compounds.

On 8th April 2003, Chemical Abstracts (CAS) registered on their database a compound with the CAS Registry Number 502143-17-1, with the chemical name "1H-Pyrazolo[3,4-b]pyridin-4-amine, N-butyl-5-(4,5-dihydro-1H-imidazol-2- yl)-1-ethyl-" and bearing the laboratory code NSC 235755. As at 5th November 2003, the CAS entry for this compound had no associated literature references and therefore it appears that no chemical synthesis and no uses of the compound have been disclosed as at 5th November 2003. The structure of the compound from the CAS database is as follows:



It is desirable to find new compounds which bind to, and preferably inhibit, phosphodiesterase type IV (PDE4).

The present invention provides a compound of formula (I) or a salt thereof (in particular, a pharmaceutically acceptable salt thereof):



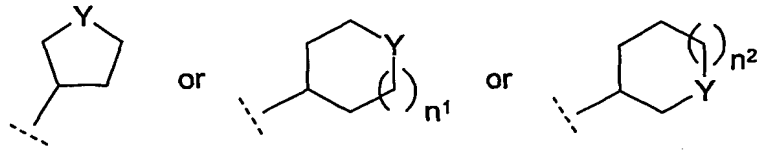
(I)

wherein:

R^1 is C_{1-4}alkyl, C_{1-3}fluoroalkyl or $-(CH_2)_2OH$;

R^2 is a hydrogen atom (H), methyl or C_1fluoroalkyl;

R^3 is optionally substituted branched C_{3-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, optionally substituted phenyl, or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc):



(aa) (bb) (cc)

in which n^1 and n^2 independently are 1 or 2; and Y is O, S, SO_2, or NR^4; where R^4 is a hydrogen atom (H), C_{1-2}alkyl, C_{1-2}fluoroalkyl, $CH_2C(O)NH_2$, $C(O)NH_2$, $C(O)$-C_{1-2}alkyl, or $C(O)$-C_1fluoroalkyl;

wherein in R^3 the optionally substituted branched C_{3-6}alkyl is optionally substituted with one or two substituents being oxo (=O), OH, C_{1-2}alkoxy or C_{1-2}fluoroalkoxy; and wherein any such substituent is not substituted at the R^3 carbon atom attached (bonded) to the -NH- group of formula (I);

wherein in R^3 the phenyl is optionally substituted with one substituent being fluoro, chloro, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy or cyano, or with two or three fluoro substituents;

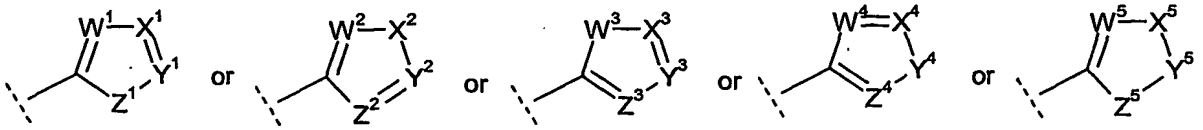
wherein in R^3 the C_{3-8}cycloalkyl or the heterocyclic group of sub-formula (aa), (bb) or (cc) is optionally substituted with one or two substituents independently being (e.g. being) oxo (=O); OH; C_{1-2}alkoxy; C_{1-2}fluoroalkoxy; NHR^{21} wherein R^{21} is a hydrogen atom (H) or C_{1-4} straight-chain alkyl; C_{1-2}alkyl; C_{1-2}fluoroalkyl (e.g. C_1fluoroalkyl such as $-CH_2F$ or $-CHF_2$); $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NHR^{22}$ wherein R^{22} is H or C_{1-2}alkyl; $-C(O)OR^{23}$ wherein R^{23} is H or C_{1-2}alkyl; $-C(O)NHR^{24}$ wherein R^{24} is H or C_{1-2}alkyl; $-C(O)R^{25}$ wherein R^{25} is C_{1-2}alkyl; fluoro; hydroxyimino (=N-OH); or (C_{1-4}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-4}alkyl); and wherein any OH, alkoxy, fluoroalkoxy or NHR^{21} substituent is not substituted at the R^3 ring carbon attached (bonded) to the -NH- group of formula (I) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc);

and wherein, when R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, then the cycloalkenyl is optionally substituted with one or two substituents independently being fluoro or C_{1-2}alkyl provided that if there are two substituents then they are not both C_2alkyl, and the R^3 ring carbon bonded to the -NH- group of formula (I) does not partake in the cycloalkenyl double bond;

and R^{3a} is a hydrogen atom (H) or straight-chain C_{1-3}alkyl;

provided that when R^{3a} is C_{1-3}alkyl then R^3 is tetrahydro-2H-pyran-4-yl, cyclohexyl (i.e. unsubstituted), 3-hydroxy-cyclohexyl, 4-oxo-cyclohexyl or 4-(hydroxyimino)cyclohexyl;

and wherein Het is of sub-formula (i), (ii), (iii), (iv) or (v):



(i) (ii) (iii) (iv) (v)

wherein:

W^1, W^2, W^4 and W^5 is N; and W^3 is NR^W ;

X^1, X^3 and X^4 is N or CR^X; X^2 is O, S or NR^X ; and X^5 is $CR^{X1}R^{X2}$ or $CR^{X3}R^{X4}$;

Y^1, Y^2 and Y^3 is CR^Y or N; Y^4 is O, S or NR^Y ; and Y^5 is $CR^{Y1}R^{Y2}$;

Z^1 and Z^5 is O, S or NR^Z; and Z^2, Z^3 and Z^4 is N or CR^Z;

wherein:

R^W is a hydrogen atom (H) or C_{1-2}alkyl;

R^X, R^{X2}, R^Y and R^{Y2} independently are:

a hydrogen atom (H);

C_{1-8}alkyl;

C_{3-6}cycloalkyl optionally substituted by one or two C_{1-2}alkyl groups and/or by one oxo (=O) group;

$-(CH_2)_n{}^{2a}$-C_{3-6}cycloalkyl optionally substituted, in the $-(CH_2)_n{}^{2a}$- moiety or in the C_{3-6}cycloalkyl moiety, by a C_{1-2}alkyl group, or optionally substituted in the C_{3-6}cycloalkyl moiety by a $-CH_2C(O)NHC_{1-2}$alkyl group, wherein n^{2a} is 1, 2 or 3;

$-(CH_2)_n{}^3-S(O)_2-R^5$, $-CH(C_{1-2}alkyl)-S(O)_2-R^5$, $-CMe_2-S(O)_2-R^5$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by $-S(O)_2-R^5$, wherein n^3 is 1 or 2;

and R^5 is C_{1-4}alkyl (e.g. C_{1-3}alkyl), $-NR^{15}R^{16}$, phenyl, carbon-linked-pyridinyl or benzyl (wherein the phenyl and benzyl are independently optionally substituted on the aromatic ring by one or two substituents independently being fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy, C_1fluoroalkoxy or OH, and wherein the pyridinyl is optionally substituted by one methyl, methoxy or OH (including any tautomer thereof));

wherein R^{15} is H, C_{1-4}alkyl (e.g. C_{1-2}alkyl), phenyl, benzyl (wherein the phenyl and benzyl are independently optionally substituted on the aromatic ring by one or two substituents independently being fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy), CH(Me)Ph, or carbon-linked-pyridinyl optionally substituted by one methyl, methoxy or OH (including any tautomer thereof);

and R^{16} is H or C_{1-2}alkyl;

or wherein R^{15} and R^{16} together are $-(CH_2)_n{}^{3a}-X^{3a}-(CH_2)_n{}^{3b}-$ in which n^{3a} and n^{3b} independently are 2 or 3 and X^{3a} is a bond, $-CH_2-$, O, or NR^{8a} wherein R^{8a} is H or C_{1-2}alkyl, acetyl, $-S(O)_2Me$ or phenyl, and wherein the ring formed by $NR^{15}R^{16}$ is optionally substituted on a ring carbon by one or two substituents independently being methyl or oxo (=O);

$-(CH_2)_n{}^4-NR^6R^7$, $-CH(C_{1-2}alkyl)-NR^6R^7$, $-CMe_2-NR^6R^7$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by $-NR^6R^7$, wherein n^4 is 0, 1, 2 or 3;

and R^6 and R^7 independently are H, C_{1-6}alkyl (e.g. C_{1-4}alkyl), C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, $-C(O)R^{17}$, $-S(O)_2R^{18}$, phenyl, benzyl (wherein the phenyl and benzyl are independently optionally substituted on the aromatic ring by one or two substituents independently being fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy), or carbon-linked-pyridinyl optionally substituted by one methyl, methoxy or OH (including any tautomer thereof);

and wherein R^{17} and R^{18} independently are C_{1-6}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl or isopropyl or n-propyl), C_{3-6}cycloalkyl, optionally substituted 5-membered heteroaryl being furyl (furanyl, e.g. 2-furyl) or 1,3-oxazolyl or isoxazolyl or oxadiazolyl or thienyl (e.g. 2- or 3- thienyl) or 1,3-thiazolyl or isothiazolyl or pyrrolyl or imidazolyl or pyrazolyl (all independently optionally substituted by one oxo and/or one or two methyl), or phenyl or benzyl (wherein the phenyl and benzyl are independently optionally substituted on the aromatic ring by one or two substituents independently

being fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy, C_1fluoroalkoxy or OH), or carbon-linked-pyridinyl optionally substituted by one methyl, methoxy or OH (including any tautomer thereof);

or R^6 and R^7 together are $-(CH_2)_{n^5}-X^5-(CH_2)_{n^6}-$ in which n^5 and n^6 independently are 2 or 3 and X^5 is a bond, $-CH_2-$, O, or NR^8 wherein R^8 is H, C_{1-2}alkyl, acetyl, $-S(O)_2Me$ or phenyl, and wherein the ring formed by NR^6R^7 is optionally substituted on a ring carbon by one or two substituents independently being methyl or oxo (=O);

$-(CH_2)_{n^7}-O-R^9$; wherein n^7 is 0, 1, 2 or 3 and R^9 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, $-C(O)R^{17}$, phenyl, or benzyl (wherein the phenyl and benzyl are independently optionally substituted on the aromatic ring by one or two of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy); wherein n^7 is 0 only when the $-(CH_2)_{n^7}-O-R^9$ is bonded to a carbon atom in the Het ring; and wherein n^7 is not 0 when Het is of sub-formula (v) (i.e. n^7 is not 0 for R^{X2} and for R^{Y2});

$-(CH_2)_{n^{11}}-C(O)-NR^{10}R^{11}$, $-CH(C_{1-2}alkyl)-C(O)-NR^{10}R^{11}$, $-CMe_2-C(O)-NR^{10}R^{11}$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by $-C(O)-NR^{10}R^{11}$, wherein n^{11} is 0, 1 or 2;

and wherein R^{10} and R^{11} independently are: H; C_{1-6}alkyl; C_{1-4}fluoroalkyl; C_{2-4}alkyl substituted by one OH or $-OC_{1-2}$alkyl other than at the connection point; C_{3-6}cycloalkyl optionally substituted by one or two methyl groups; $-CH_2-C_{3-6}$cycloalkyl optionally substituted by one methyl, NH_2 or NHMe group; $-(CH_2)_{n^{17}}-Het^2$; carbon-linked-pyridinyl optionally substituted by one methyl, methoxy or OH (including any tautomer thereof); phenyl; benzyl; or $-CH(C_{1-2}alkyl)Ph$ [wherein the phenyl, benzyl, and $-CH(C_{1-2}alkyl)Ph$ are independently optionally substituted on the aromatic ring by one or two substituents independently being: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy, C_1fluoroalkoxy, OH, $-NR^{10a}R^{10b}$ (wherein R^{10a} is H or C_{1-2}alkyl and R^{10b} is H, C_{1-2}alkyl, $-C(O)-C_{1-2}$alkyl or $-S(O)_2-C_{1-2}$alkyl), $-C(O)-NR^{10c}R^{10d}$ (wherein R^{10c} and R^{10d} independently are H or C_{1-2}alkyl), or $-S(O)_2-R^{10e}$ (wherein R^{10e} is C_{1-2}alkyl, NH_2, NHMe or NMe_2)],

wherein n^{17} is 0, 1 or 2 and wherein Het^2 is a 4-, 5- or 6- membered saturated heterocyclic ring containing one O or S ring atom or one NR^{27} ring group wherein R^{27} is H, C_{1-2}alkyl, -C(O)Me, or $-S(O)_2Me$, wherein the Het^2 ring is optionally substituted on a ring carbon by one or two substituents independently being methyl or oxo (=O);

and wherein when n^{17} is 2 then the Het^2 ring can optionally contain one additional ring N atom at the Het^2 ring position bonded to the $-(CH_2)_n{}^{17}-$ moiety; provided that, when Het^2 contains one O or S or NR^{27} ring atom/group and one additional ring N atom, then the O/S/NR^{27} ring atom/group and the one additional ring N atom are not directly bonded to each other, and are separated by more than one carbon atom;

or R^{10} and R^{11} together are $-(CH_2)_n{}^8-X^6-(CH_2)_n{}^9-$ in which n^8 and n^9 independently are 2 or 3 and X^6 is a bond, $-CH_2-$, O, or NR^{12} wherein R^{12} is H, C_{1-2}alkyl, acetyl, $-S(O)_2Me$ or phenyl, and wherein the ring formed by $NR^{10}R^{11}$ is optionally substituted on a ring carbon by one or two substituents independently being methyl or oxo (=O);

$-(CH_2)_n{}^{12}-C(O)-OR^{13}$ wherein n^{12} is 0, 1 or 2; and wherein R^{13} is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, phenyl, or benzyl (wherein the phenyl and benzyl are independently optionally substituted on the aromatic ring by one or two of (independently) fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy);

$-(CH_2)_n{}^{13}-C(O)-R^{13a}$ wherein n^{13} is 0, 1 or 2; and wherein R^{13a} is a hydrogen atom (H), C_{1-6}alkyl, C_{1-2}fluoroalkyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, benzyl, or phenyl; wherein the phenyl and benzyl are independently optionally substituted on the aromatic ring by one or two of (independently) fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

$-(CH_2)_n{}^{14}-Het^1$, $-CH(C_{1-2}alkyl)-Het^1$, $-CMe_2-Het^1$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by Het^1, wherein n^{14} is 0, 1 or 2 and wherein Het^1 is a 4-, 5-, 6- or 7-membered saturated heterocyclic ring;

wherein said heterocyclic ring Het^1 contains one O or S ring atom and/or one NR^{14} ring group wherein R^{14} is H, C_{1-4}alkyl, C_{3-6}cycloalkyl, benzyl, phenyl, $-C(O)R^{19}$, or $-S(O)_2R^{19}$;

wherein R^{19}, independent of any other R^{19}, is C_{1-6}alkyl (e.g. C_{1-4}alkyl or C_{1-3}alkyl), C_{3-6}cycloalkyl, thienyl (e.g. 2-thienyl), furyl (furanyl, e.g. furan-2-yl), or phenyl or benzyl; wherein the phenyl and benzyl are independently optionally substituted by one or two of (independently) fluoro, methyl or methoxy;

and wherein said heterocyclic ring Het^1 is optionally substituted (at a position or positions other than any NR^{14} position) by one or two oxo (=O) and/or one C_{1-4}alkyl substituents;

provided that, when the heterocyclic ring Het^1 contains one O or S ring atom and one NR^{14} ring group then: (a) the O/S ring atom and the NR^{14} ring group are not directly bonded to each other, and (b) the O/S ring atom and the

NR^{14} ring group are separated by more than one carbon atom unless Het^1 contains an $-NR^{14}-C(O)-O-$ or $-NR^{14}-C(O)-S-$ moiety as part of the ring; or $-(CH_2)_n{}^{10}-Ar$, $-CH(C_{1-2}alkyl)-Ar$, $-CMe_2-Ar$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by Ar, wherein n^{10} is 0, 1 or 2 and

(i) Ar is phenyl optionally substituted by one or two substituents independently being fluoro, chloro, bromo, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy, OH, $-NR^{11a}R^{11b}$ (wherein R^{11a} is H or C_{1-2}alkyl and R^{11b} is H, C_{1-2}alkyl, $-C(O)-C_{1-2}$alkyl or $-S(O)_2-C_{1-2}$alkyl), cyano, $-C(O)-NR^{11c}R^{11d}$ (wherein R^{11c} and R^{11d} independently are H or C_{1-2}alkyl), $-C(O)-OR^{11e}$ wherein R^{11e} is H or C_{1-2}alkyl, or $-S(O)_2-R^{11f}$ (wherein R^{11f} is C_{1-2}alkyl, NH_2, NHMe or NMe_2); or the phenyl Ar is optionally substituted at two adjacent Ar ring atoms by the two ends of a chain which is: $-(CH_2)_4-$, $-(CH_2)_3-$, or $-CH=CH-CH=CH-$; or

(ii) Ar is an optionally substituted 5- or 6-membered heterocyclic aromatic ring containing 1, 2, 3 or 4 heteroatoms (e.g. 1, 2 or 3 heteroatoms) selected from O, N or S; and wherein when the heterocyclic aromatic ring Ar contains 2, 3 or 4 heteroatoms (e.g. 2 or 3 heteroatoms), one is selected from O, N and S and the remaining heteroatom(s) are N; and wherein the heterocyclic aromatic ring Ar is optionally substituted by one or two groups independently being C_{1-4}alkyl (e.g. C_{1-2}alkyl) or OH (including any keto tautomer of an OH-substituted aromatic ring), or the heterocyclic aromatic ring Ar is optionally substituted at two adjacent Ar ring atoms by the two ends of a chain which is: $-(CH_2)_4-$, $-(CH_2)_3-$, or $-CH=CH-CH=CH-$;

R^{X1} and R^{Y1} independently are a hydrogen atom (H), C_{1-2}alkyl or C_1fluoroalkyl;

R^{X3} and R^{X4} together are $-(CH_2)_n{}^{15}-X^7-(CH_2)_n{}^{16}-$ wherein n^{15} and n^{16} independently are 1 or 2 and X^7 is a bond, $-CH_2-$, O, or NR^{X5} wherein R^{X5} is H, C_{1-2}alkyl, acetyl or $-S(O)_2Me$; and

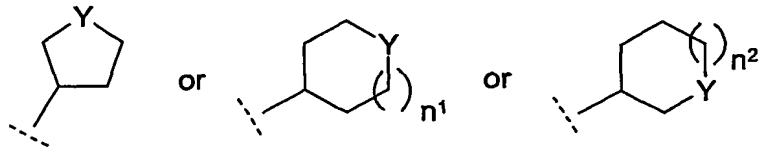
R^Z is a hydrogen atom (H) or C_{1-2}alkyl,

provided that:
when R^3 is the heterocyclic group of sub-formula (bb), n^1 is 1, and Y is NR^4, then R^4 is not C_{1-2}alkyl, C_{1-2}fluoroalkyl or $CH_2C(O)NH_2$.

Preferably, R^{3a} is a hydrogen atom (H) or methyl.

It is particularly preferred that R^{3a} is a hydrogen atom (H).

In one optional embodiment of the invention, R^3 is optionally substituted branched C_{3-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted phenyl, or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc):



(aa) (bb) (cc)

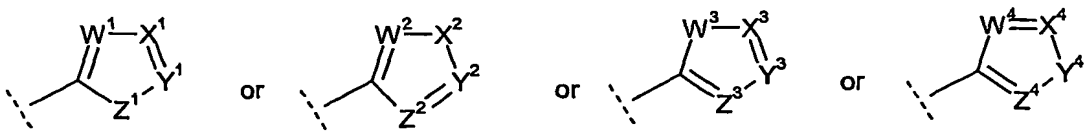
in which n^1 and n^2 are 1 or 2; and Y is O, S, SO_2, or NR^4; where R^4 is a hydrogen atom, C_{1-2}alkyl, C_{1-2}fluoroalkyl, $C(O)NH_2$, $C(O)$-C_{1-2}alkyl, or $C(O)$-C_1fluoroalkyl; provided that Y is not NR^4 when the heterocyclic group is of sub-formula (aa).

Alternatively or additionally, in one optional embodiment of the invention, in R^3 the branched C_{3-6}alkyl is optionally substituted with one or two substituents being oxo (=O), OH, C_{1-2}alkoxy or C_{1-2}fluoroalkoxy; and wherein any such substituent is not substituted at the R^3 carbon atom attached to the -NH- group of formula (I).

Alternatively or additionally, in one optional embodiment of the invention, in R^3 the phenyl is optionally substituted with one substituent being fluoro, chloro, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy or cyano.

Alternatively or additionally, in one optional embodiment of the invention, in R^3 the C_{3-8}cycloalkyl or the heterocyclic group of sub-formula (aa), (bb) or (cc) is optionally substituted with one or two substituents being oxo (=O), OH, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy, or C_{1-2}alkyl; and wherein any OH, alkoxy or fluoroalkoxy substituent is not substituted at the R^3 ring carbon attached to the -NH- group of formula (I) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc).

Alternatively or additionally, in one optional embodiment of the invention, Het is of sub-formula (i), (ii), (iii) or (iv):



(i) (ii) (iii) (iv)

wherein:
W^1, W^2 and W^4 is N; and W^3 is NR^W;
X^1, X^3 and X^4 is N or CR^X; and X^2 is O, S or NR^X;
Y^1, Y^2 and Y^3 is CR^Y or N; and Y^4 is O, S or NR^Y;
Z^1 is O, S or NR^Z; and Z^2, Z^3 and Z^4 is N or CR^Z;

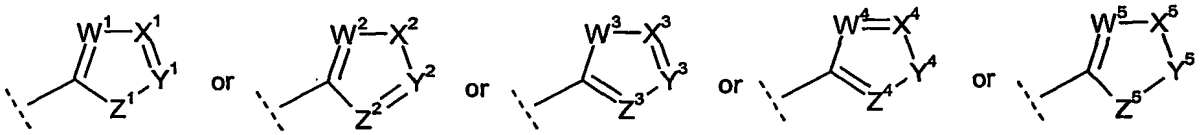
and wherein:
R^W is a hydrogen atom (H) or C_{1-2}alkyl; and
R^Z is a hydrogen atom (H) or C_{1-2}alkyl.

Alternatively or additionally, in one optional embodiment of the invention, R^X and R^Y independently are:

a hydrogen atom (H);
C_{1-8}alkyl;
C_{3-6}cycloalkyl;
$-(CH_2)_{n^3}-SO_2-R^5$ wherein n^3 is 1 or 2 and R^5 is C_{1-3}alkyl or $-NH-C_{1-2}$alkyl;
$-(CH_2)_{n^4}-NR^6R^7$ wherein n^4 is 0, 1 or 2, and R^6 and R^7 independently are H, C_{1-6}alkyl e.g. C_{1-4}alkyl, $-C(O)-C_{1-2}$alkyl or $-SO_2-C_{1-2}$alkyl; or R^6 and R^7 together are $-(CH_2)_{n^5}-X^5-(CH_2)_{n^6}-$ in which n^5 and n^6 independently are 2 or 3 and X^5 is a bond, $-CH_2-$, O, or NR^8 wherein R^8 is H or C_{1-2}alkyl;
$-(CH_2)_{n^7}-O-R^9$ wherein n^7 is 1 or 2 and R^9 is H or C_{1-6}alkyl;
$-C(O)-NR^{10}R^{11}$ wherein R^{10} and R^{11} independently are H or C_{1-6}alkyl; or R^{10} and R^{11} together are $-(CH_2)_{n^8}-X^6-(CH_2)_{n^9}-$ in which n^8 and n^9 independently are 2 or 3 and X^6 is a bond, $-CH_2-$, O, or NR^{12} wherein R^{12} is H or C_{1-2}alkyl;
$-C(O)-OR^{13}$ wherein R^{13} is H or C_{1-6}alkyl;
a 4-, 5-, 6- or 7-membered saturated heterocyclic ring containing one O ring atom or one NR^{14} ring group wherein R^{14} is H or C_{1-4}alkyl, said heterocyclic ring being optionally substituted (at a position or positions other than any NR^{14} position) by one oxo (=O) and/or one C_{1-4}alkyl substituent; or
$-(CH_2)_{n^{10}}-Ar$ wherein n^{10} is 0, 1 or 2 and
(i) Ar is phenyl optionally substituted by one or two substituents being fluoro, chloro, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy or cyano; or
(ii) Ar is an optionally substituted 5- or 6-membered heterocyclic aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N or S; and wherein when the heterocyclic aromatic ring Ar contains 2 or 3 heteroatoms, one is selected from O, N and S and the remaining heteroatom(s) are N; and wherein

the heterocyclic aromatic ring Ar is optionally substituted by one or two C_{1-4}alkyl groups.

Alternatively or additionally, in one optional embodiment of the invention, Het is of sub-formula (i), (ii), (iii), (iv) or (v):



(i) (ii) (iii) (iv) (v)

wherein:
W^1, W^2, W^4 and W^5 is N; and W^3 is NR^W;
X^1, X^3 and X^4 is N or CR^X; X^2 is O, S or NR^X; and X^5 is $CR^{X1}R^{X2}$;
Y^1, Y^2 and Y^3 is CR^Y or N; Y^4 is O, S or NR^Y; and Y^5 is $CR^{Y1}R^{Y2}$;
Z^1 and Z^5 is O, S or NR^Z; and Z^2, Z^3 and Z^4 is N or CR^Z;

and wherein:
R^W is a hydrogen atom (H) or C_{1-2}alkyl; and
R^Z is a hydrogen atom (H) or C_{1-2}alkyl.

In one optional embodiment of the invention, R^X, R^{X2}, R^Y and R^{Y2} independently are, or R^X and R^Y independently are:
- a hydrogen atom (H);
- C_{1-8}alkyl;
- C_{3-6}cycloalkyl optionally substituted by a C_{1-2}alkyl group;
- $-(CH_2)_n{}^{2a}-C_{3-6}$cycloalkyl optionally substituted, in the $-(CH_2)_n{}^{2a}-$ moiety or in the C_{3-6}cycloalkyl moiety, by a C_{1-2}alkyl group, wherein n^{2a} is 1, 2 or 3;
- $-(CH_2)_n{}^3-SO_2-R^5$ wherein n^3 is 1 or 2 and R^5 is C_{1-3}alkyl or $-NH-C_{1-2}$alkyl or phenyl;
- $-(CH_2)_n{}^4-NR^6R^7$ wherein n^4 is 0, 1, 2 or 3, and R^6 and R^7 independently are H, C_{1-6}alkyl e.g. C_{1-4}alkyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, $-C(O)-C_{1-2}$alkyl, $-SO_2-C_{1-2}$alkyl, phenyl, or benzyl (wherein the phenyl or benzyl are independently optionally substituted on the aromatic ring by one of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy); or R^6 and R^7 together are $-(CH_2)_n{}^5-X^5-(CH_2)_n{}^6-$ in which n^5 and n^6 independently are 2 or 3 and X^5 is a bond, $-CH_2-$, O, or NR^8 wherein R^8 is H or C_{1-2}alkyl;

$-(CH_2)_{n^7}$-O-R^9; wherein n^7 is 0, 1, 2 or 3 and R^9 is H or C_{1-6}alkyl; wherein n^7 is 0 only when the $-(CH_2)_{n^7}$-O-R^9 is bonded to a carbon atom in the Het ring; and wherein n^7 is not 0 when Het is of sub-formula (v) (i.e. n^7 is not 0 for R^{X2} and for R^{Y2});

$-C(O)-NR^{10}R^{11}$ wherein R^{10} and R^{11} independently are H, C_{1-6}alkyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, phenyl, or benzyl (wherein the phenyl or benzyl are independently optionally substituted on the aromatic ring by one of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy); or R^{10} and R^{11} together are $-(CH_2)_{n^8}$-X^6-$(CH_2)_{n^9}$- in which n^8 and n^9 independently are 2 or 3 and X^6 is a bond, $-CH_2-$, O, or NR^{12} wherein R^{12} is H or C_{1-2}alkyl;

$-C(O)-OR^{13}$ wherein R^{13} is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, phenyl, or benzyl (wherein the phenyl or benzyl are independently optionally substituted on the aromatic ring by one of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy);

$-C(O)-R^{13a}$ wherein R^{13a} is a hydrogen atom (H), C_{1-6}alkyl, C_{1-2}fluoroalkyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, benzyl, or phenyl; wherein the phenyl or benzyl are independently optionally substituted on the aromatic ring by one of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

a 4-, 5-, 6- or 7-membered saturated heterocyclic ring containing one O ring atom or one NR^{14} ring group wherein R^{14} is H or C_{1-4}alkyl, said heterocyclic ring being optionally substituted (at a position or positions other than any NR^{14} position) by one oxo (=O) and/or one C_{1-4}alkyl substituent; or

$-(CH_2)_{n^{10}}$-Ar wherein n^{10} is 0, 1 or 2 and

(i) Ar is phenyl optionally substituted by one or two substituents being fluoro, chloro, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy or cyano;

or

(ii) Ar is an optionally substituted 5- or 6-membered heterocyclic aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N or S; and wherein when the heterocyclic aromatic ring Ar contains 2 or 3 heteroatoms, one is selected from O, N and S and the remaining heteroatom(s) are N; and wherein the heterocyclic aromatic ring Ar is optionally substituted by one or two C_{1-4}alkyl groups; and

R^{X1} and R^{Y1} independently are a hydrogen atom (H), C_{1-2}alkyl or C_1fluoroalkyl.

In compounds, for example in the compounds of formula (I), an "alkyl" group or moiety may be straight-chain or branched. Alkyl groups, for example C_{1-8}alkyl or

C_{1-6}alkyl or C_{1-4}alkyl or C_{1-3}alkyl or C_{1-2}alkyl, which may be employed include C_{1-6}alkyl or C_{1-4}alkyl or C_{1-3}alkyl or C_{1-2}alkyl such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, or n-hexyl, or any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, isobutyl, 3-methylbutan-2-yl, 2-ethylbutan-1-yl, or the like.

A corresponding meaning is intended for "alkoxy", "alkylene", and like terms derived from alkyl. For example, "alkoxy" such as C_{1-6}alkoxy or C_{1-4}alkoxy or C_{1-2}alkoxy includes methoxy, ethoxy, propyloxy, and oxy derivatives of the alkyls listed above. "Alkylsulfonyl" such as C_{1-4}alkylsulfonyl includes methylsulfonyl (methanesulfonyl), ethylsulfonyl, and others derived from the alkyls listed above. "Alkylsulfonyloxy" such as C_{1-4}alkylsulfonyloxy includes methanesulfonyloxy (methylsulfonyloxy), ethanesulfonyloxy, *et al.*

"Cycloalkyl", for example C_{3-8}cycloalkyl, includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Preferably, a C_{3-8} cycloalkyl group is C_{3-6}cycloalkyl or C_{5-6}cycloalkyl, that is the cycloalkyl group contains a 3-6 membered or 5-6 membered carbocyclic ring respectively.

"Fluoroalkyl" includes alkyl groups with one, two, three, four, five or more fluorine substituents, for example C_{1-4}fluoroalkyl or C_{1-3}fluoroalkyl or C_{1-2}fluoroalkyl such as monofluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl (CF_3CH_2-), 2,2-difluoroethyl (CHF_2-CH_2-), or 2-fluoroethyl (CH_2F-CH_2-), etc. "Fluoroalkoxy" includes C_{1-4}fluoroalkoxy or C_{1-2}fluoroalkoxy such as trifluoromethoxy, pentafluoroethoxy, monofluoromethoxy, difluoromethoxy, etc. "Fluoroalkylsulfonyl" such as C_{1-4}fluoroalkylsulfonyl includes trifluoromethanesulfonyl, pentafluoroethylsulfonyl, etc.

A halogen atom ("halo") present in compounds, for example in the compounds of formula (I), can be a fluorine, chlorine, bromine or iodine atom ("fluoro", "chloro", "bromo" or "iodo").

When the specification states that atom or moiety A is "bonded" or "attached" to atom or moiety B, it means that atom/moiety A is directly bonded to atom/moiety B usually by means of one or more covalent bonds, and excludes A being indirectly attached to B via one or more intermediate atoms/moieties (e.g. excludes A-C-B); unless it is clear from the context that another meaning is intended.

By "carbon-linked-pyridinyl" is meant pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl.

Preferably, R^1 is C_{1-3}alkyl, C_{1-3}fluoroalkyl or -$(CH_2)_2OH$; more preferably C_{1-3}alkyl, C_{1-2}fluoroalkyl or -$(CH_2)_2OH$; still more preferably C_{2-3}alkyl, C_2fluoroalkyl or -$(CH_2)_2OH$; and yet more preferably C_2alkyl or C_2fluoroalkyl. When R^1 is C_{1-4}alkyl or C_{1-3}fluoroalkyl, it can be straight-chained or branched. R^1 can for example be methyl, trifluoromethyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, C_2fluoroalkyl or -$(CH_2)_2OH$; and more preferably R^1 is ethyl, n-propyl, C_2fluoroalkyl (e.g. C_1fluoroalkyl-CH_2- such as CF_3-CH_2-) or -$(CH_2)_2OH$. R^1 is most preferably ethyl.

Preferably, R^2 is a hydrogen atom (H) or methyl, more preferably a hydrogen atom (H).

Where R^3 optionally substituted phenyl, preferably the phenyl is optionally substituted with one substituent being fluoro, chloro, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy or cyano. Where R^3 is optionally substituted phenyl, the optional substituent can be at the 2-, 3- or 4-position of the phenyl ring, e.g. at the 4-position. For example, R^3 can be phenyl or fluorophenyl; in particular 4-fluorophenyl.

R^3 is preferably optionally substituted branched C_{3-6}alkyl, optionally substituted C_{3-8}cycloalkyl, or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc). R^3 is more preferably optionally substituted C_{3-8}cycloalkyl, or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc).

Preferably, in R^3 there is one substituent or no substituent.

Where R^3 is optionally substituted branched C_{3-6}alkyl, then preferably R^3 is optionally substituted branched C_{4-5}alkyl and/or unsubstituted C_{3-6}alkyl such as isopropyl, isobutyl, sec-butyl, t-butyl, 3-methylbutan-2-yl, or 2-ethylbutan-1-yl. Where R^3 is optionally substituted branched C_{3-6}alkyl, it is most preferably isobutyl, sec-butyl, t-butyl or 3-methylbutan-2-yl (for example (R)-3-methylbutan-2-yl or (S)-3-methylbutan-2-yl).

In one optional embodiment, where R^3 is optionally substituted C_{3-8}cycloalkyl, it is not optionally substituted C_5cycloalkyl, i.e. not optionally substituted cyclopentyl. In this case, more preferably, R^3 is optionally substituted C_{6-8}cycloalkyl or optionally substituted C_{6-7}cycloalkyl.

Where R^3 is optionally substituted C_{3-8}cycloalkyl, it is more preferably optionally substituted C_6cycloalkyl (i.e. optionally substituted cyclohexyl); for example C_6cycloalkyl optionally substituted with one or two substituents independently being (e.g. being) oxo (=O), OH, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy (e.g. trifluoromethoxy), or C_{1-2}alkyl, and wherein any OH, alkoxy or fluoroalkoxy substituent is not substituted at the R^3 ring carbon attached (bonded) to the -NH- group of formula (I).

Where R^3 is optionally substituted C_{3-8}cycloalkyl, the one or two optional substituents preferably comprise (e.g. is or independently are (e.g. is or are)) oxo (=O); OH; C_1alkoxy; C_1fluoroalkoxy (e.g. trifluoromethoxy); NHR^{21} wherein R^{21} is a hydrogen atom (H) or C_{1-2} straight-chain alkyl; C_{1-2}alkyl such as methyl; C_1fluoroalkyl such as

$-CH_2F$ or $-CHF_2$; $-CH_2OH$; $-CH_2NHR^{22}$ wherein R^{22} is H; $-C(O)OR^{23}$ wherein R^{23} is H or methyl; $-C(O)NHR^{24}$ wherein R^{24} is H or methyl; $-C(O)R^{25}$ wherein R^{25} is methyl; fluoro; hydroxyimino (=N-OH); or (C_{1-2}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-2}alkyl); and wherein any OH, alkoxy, fluoroalkoxy or NHR^{21} substituent is not substituted at the R^3 ring carbon attached (bonded) to the -NH- group of formula (I) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc).

More preferably, where R^3 is optionally substituted C_{3-8}cycloalkyl, the one or two optional substituents comprise (e.g. is or independently are (e.g. is or are)) oxo (=O); OH; NHR^{21} wherein R^{21} is a hydrogen atom (H); C_{1-2}alkyl such as methyl; C_1fluoroalkyl such as $-CH_2F$ or $-CHF_2$; $-C(O)OR^{23}$ wherein R^{23} is H or methyl; $-C(O)NHR^{24}$ wherein R^{24} is H or methyl; fluoro; hydroxyimino (=N-OH); or (C_{1-2}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-2}alkyl).

Still more preferably, where R^3 is optionally substituted C_{3-8}cycloalkyl, the one or two optional substituents comprise (e.g. is or independently are (e.g. is or are)) oxo (=O); OH; NHR^{21} wherein R^{21} is a hydrogen atom (H); methyl; $-CH_2F$; $-CHF_2$; $-C(O)OR^{23}$ wherein R^{23} is H; fluoro; hydroxyimino (=N-OH); or (C_{1-2}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-2}alkyl). Yet more preferably, where R^3 is optionally substituted C_{3-8}cycloalkyl, the one or two optional substituents comprise (e.g. is or independently are (e.g. is or are)) oxo (=O); OH; methyl; fluoro; hydroxyimino (=N-OH); or (C_{1-2}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-2}alkyl).

Most preferably, where R^3 is optionally substituted C_{3-8}cycloalkyl, the one or two optional substituents comprise (e.g. is or independently are (e.g. is or are)) OH, oxo (=O) or hydroxyimino (=N-OH). For example, where R^3 is optionally substituted C_{3-8}cycloalkyl, the one or two optional substituents preferably comprise (e.g. is or are) OH and/or oxo (=O).

Optionally, in R^3, the C_{3-8}cycloalkyl is unsubstituted.

Where R^3 is optionally substituted C_{3-8}cycloalkyl, e.g. optionally substituted C_{5-8}cycloalkyl such as optionally substituted C_6cycloalkyl (optionally substituted cyclohexyl), the one or two optional substituents if present preferably comprise a substituent (for example is or are substituent(s)) at the 3-, 4- or 5- position(s) of the R^3 cycloalkyl ring. (In this connection, the 1-position of the R^3 cycloalkyl ring is deemed to be the connection point to the -NH- in formula (I)).

Where R^3 is optionally substituted C_{3-8}cycloalkyl, any OH, alkoxy, fluoroalkoxy, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NHR^{22}$, $-C(O)OR^{23}$, $-C(O)NHR^{24}$, $-C(O)R^{25}$ or fluoro substituent (particularly any OH substituent) is more preferably at the 3-, 4- or 5-position, e.g. the 3- or 5-position, of the R^3 cycloalkyl (e.g. C_{6-8}cycloalkyl) ring. For example, any OH, alkoxy, fluoroalkoxy, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NHR^{22}$, $-C(O)OR^{23}$, $-C(O)NHR^{24}$, $-C(O)R^{25}$ or fluoro substituent (particularly any OH substituent) can be at the 3-position of a R^3 C_5cycloalkyl (cyclopentyl) ring or at the 3-, 4- or 5- position, e.g. 3- or 5-position, of a R^3 C_6cycloalkyl (cyclohexyl) ring. (In this connection, and also below, the 1-position of the R^3 cycloalkyl ring is deemed to be the connection point to the -NH- in formula (I)).

Where R^3 is optionally substituted C_{3-8}cycloalkyl, any NHR^{21} substituent is preferably at the 2-, 3-, 4- or 5- position, preferably the 2- or 3-position or more preferably the 3-position, of the R^3 cycloalkyl (e.g. C_{6-8}cycloalkyl e.g. cyclohexyl) ring.

Where R^3 is optionally substituted C_{3-8}cycloalkyl, any alkyl or fluoroalkyl substituent is preferably at the 1-, 2-, 3-, 4- or 5- position, more preferably the 1-, 2-, 3- or 5-position, still more preferably the 1- or 3-position, of the R^3 cycloalkyl (e.g. C_{6-8}cycloalkyl e.g. cyclohexyl) ring.

Where R^3 is optionally substituted C_{3-8}cycloalkyl, any oxo (=O), hydroxyimino (=N-OH); or (C_{1-4}alkoxy)imino (=N-OR^{26}) substituent is preferably at the 3- or 4-position, preferably at the 4-position, of the R^3 cycloalkyl (e.g. C_{6-8}cycloalkyl e.g. cyclohexyl) ring.

Where R^3 is optionally substituted C_{3-8}cycloalkyl, R^3 is preferably cyclohexyl (i.e. unsubstituted) or cyclohexyl substituted by one oxo (=O), OH, NHR^{21}, C_{1-2}alkyl, C_{1-2}fluoroalkyl, $-CH_2OH$, $-C(O)OR^{23}$, $-C(O)NHR^{24}$, $-C(O)R^{25}$, fluoro, hydroxyimino (=N-OH) or (C_{1-4}alkoxy)imino (=N-OR^{26}) substituent, or cyclohexyl substituted by two fluoro substituents. More preferably, R^3 is cyclohexyl (i.e. unsubstituted), or cyclohexyl substituted by one oxo (=O), OH, NHR^{21}, C_{1-2}alkyl, C_{1-2}fluoroalkyl, $-C(O)OR^{23}$, fluoro, hydroxyimino (=N-OH) or (C_{1-4}alkoxy)imino (=N-OR^{26}) substituent, or cyclohexyl substituted by two fluoro substituents. Still more preferably R^3 is cyclohexyl (i.e. unsubstituted) or cyclohexyl substituted by one oxo (=O), hydroxyimino (=N-OH), C_{1-2}alkyl or OH substituent, for example R^3 can be cyclohexyl (i.e. unsubstituted) or cyclohexyl substituted by one oxo (=O) or OH substituent. The optional substituent can

be at the 3- or 4- position, e.g. 3-position, of the R^3 cyclohexyl ring; more preferably any OH substituent is preferably at the 3-position of the R^3 cyclohexyl ring, and/or any oxo (=O), hydroxyimino (=N-OH) or (C_{1-4}alkoxy)imino (=N-OR^{26}) substituent is preferably at the 4-position of the R^3 cyclohexyl ring.

Where R^3 is optionally substituted C_6cycloalkyl, R^3 can for example be 4-hydroxy-cyclohexyl (i.e. 4-hydroxycyclohexan-1-yl) or 3-oxo-cyclohexyl, but R^3 is more preferably cyclohexyl (i.e. unsubstituted), 3-hydroxy-cyclohexyl (i.e. 3-hydroxycyclohexan-1-yl), 4-oxo-cyclohexyl (i.e. 4-oxocyclohexan-1-yl), 4-(hydroxyimino)cyclohexyl (i.e. 4-(hydroxyimino)cyclohexan-1-yl), 4-(C_{1-2}alkoxyimino)cyclohexyl, 1-methylcyclohexyl or 3-methylcyclohexyl. In one embodiment, R^3 can optionally be cyclohexyl (i.e. unsubstituted) or 3-hydroxy-cyclohexyl or 4-oxo-cyclohexyl. Where R^3 is optionally substituted C_6cycloalkyl, R^3 is most preferably cyclohexyl (i.e. unsubstituted), 4-oxo-cyclohexyl (i.e. 4-oxocyclohexan-1-yl) or 4-(hydroxyimino)cyclohexyl (i.e. 4-(hydroxyimino)cyclohexan-1-yl).

Where R^3 is optionally substituted C_5cycloalkyl (optionally substituted cyclopentyl), R^3 can for example be cyclopentyl (i.e. unsubstituted) or 3-hydroxy-cyclopentyl.

Where R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, preferably it is optionally substituted mono-unsaturated-C_{5-6}cycloalkenyl, more preferably optionally substituted mono-unsaturated-C_6cycloalkenyl (i.e. optionally substituted mono-unsaturated-cyclohexenyl = optionally substituted cyclohexenyl). Still more preferably, the R^3 cyclohexenyl is optionally substituted cyclohex-3-en-1-yl.

Where R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, preferably the R^3 cycloalkenyl is optionally substituted with one or two substituents independently being fluoro or methyl; preferably if there are two substituents then they are not both methyl. Preferably, the R^3 cycloalkenyl is optionally substituted with one substituent being fluoro or C_{1-2}alkyl (e.g. methyl); more preferably the R^3 cycloalkenyl is substituted with one fluoro substituent or is unsubstituted. For R^3 cycloalkenyl, the optional substituent(s) can be at the 1-, 2-, 3-, 4- or 5- position(s) of the cycloalkenyl ring.

Where R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then Y is preferably O, S, SO_2, NH or N-C(O)-Me (for example O, S, SO_2 or N-C(O)-Me), more preferably O, NH or N-C(O)-Me, still more preferably O or N-C(O)-Me, most preferably O. (When Y is NH or N-C(O)-Me, then R^4 is H or -C(O)-Me).

Preferably, R^4 is a hydrogen atom (H), C_{1-2}alkyl, $C(O)NH_2$, C(O)-Me or $C(O)-CF_3$. Optionally, R^4 can be a hydrogen atom (H), C_{1-2}alkyl, C(O)-Me or $C(O)-CF_3$, more preferably H, C(O)-Me or $C(O)-CF_3$, still more preferably H or C(O)-Me.

Preferably, Y is not N-C(O)-Me when the heterocyclic group is of sub-formula (aa).

Where R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then it is preferable that R^3 is the heterocyclic group of sub-formula (aa) or (bb). More preferably, in R^3, the heterocyclic group is of sub-formula (bb).

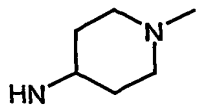
In sub-formula (bb), n^1 is preferably 1. In sub-formula (cc), n^2 is preferably 1. That is, six-membered rings are preferred in the R^3 heterocyclic group.

Preferably, in R^3, the heterocyclic group of sub-formula (aa), (bb) or (cc) is unsubstituted. (In this connection, where Y is NR^4, R^4 is not classified as a substituent).

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), the one or two optional substituents preferably comprise (e.g. is or independently are (e.g. is or are)): OH; oxo (=O); C_{1-2}alkyl (e.g. methyl) or C_{1-2}fluoroalkyl (e.g. C_1fluoroalkyl such as $-CH_2F$ or $-CHF_2$). More preferably, in the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), the one or two optional substituents comprise (e.g. is or independently are ((e.g. is or are)) OH and/or oxo; most preferably the one or two optional substituents comprise (e.g. is or are) oxo (=O). In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any oxo (=O) substituents are preferably on a carbon atom bonded (adjacent) to X, and/or can be at the 2-, 3-, 4- or 5- position(s) of the R^3 heterocyclic ring. (In this connection, the 1-position of the R^3 heterocyclic ring is deemed to be the connection point to the -NH- in formula (I)). Preferably, only C_{1-2}alkyl, C_{1-2}fluoroalkyl, fluoro or oxo (=O) substitution or no substitution is allowed at each of the 2- and 6-positions of the R^3 heterocyclic ring.

When R^3 is the heterocyclic group of sub-formula (aa) and Y is NR^4, then preferably R^4 is not C(O)-Me. More preferably, when R^3 is the heterocyclic group of sub-formula (aa) and Y is NR^4, then R^4 is preferably not C(O)R, i.e. or e.g. R^4 is preferably not $C(O)NH_2$, $C(O)-C_{1-2}$alkyl or $C(O)-C_1$fluoroalkyl. In one embodiment, Y is O, S, SO_2 or NH when R^3 is the heterocyclic group of sub-formula (aa).

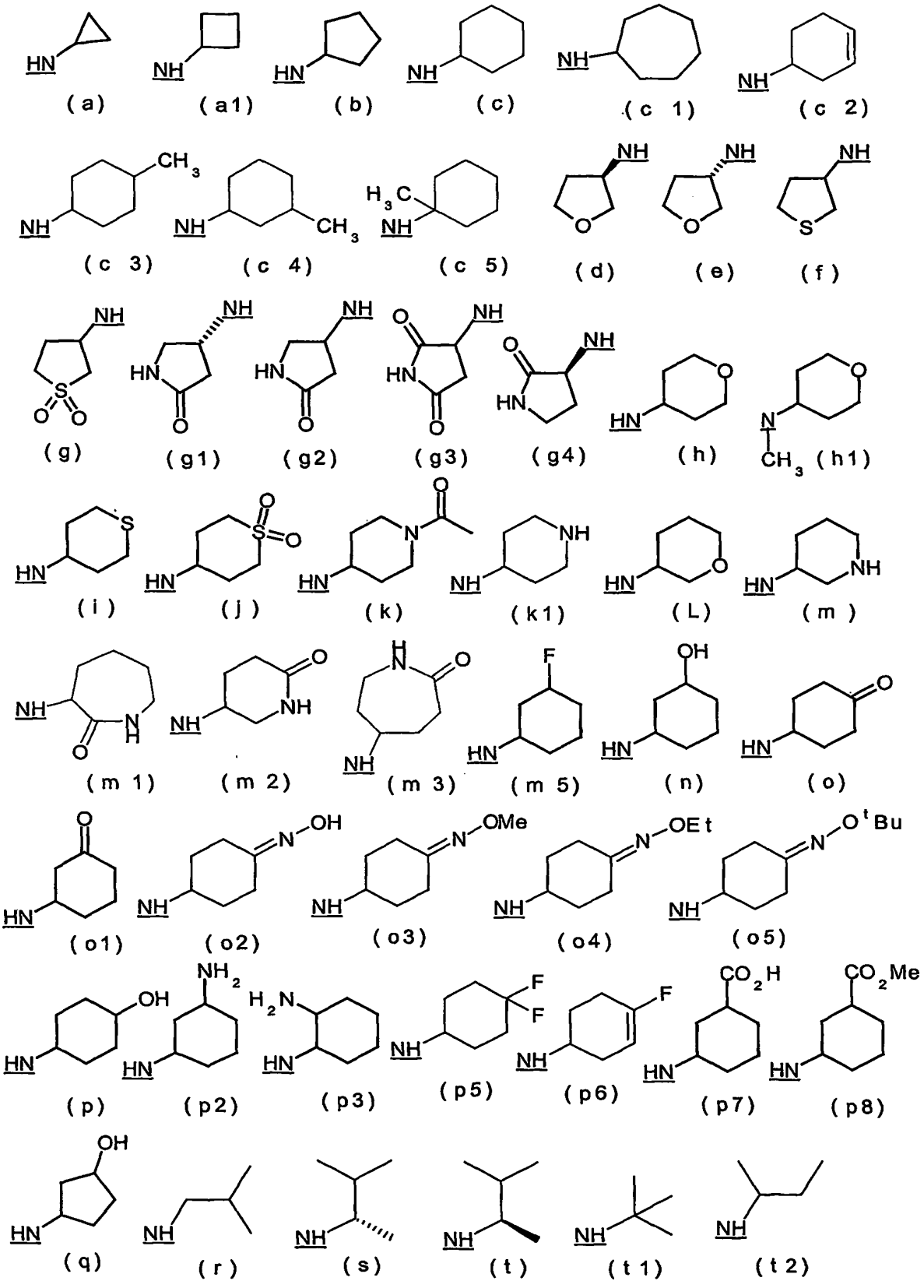
When R^3 is the heterocyclic group of sub-formula (aa), preferably Y is not NR^4.

Optionally, according to one embodiment of the invention, NHR^3 or NR^3R^{3a} is not 

. More preferably, when R^3 is the heterocyclic group of sub-formula (bb)

and Y is NR^4, and optionally when n^1 is 1, then preferably R^4 is not methyl. More preferably, when R^3 is the heterocyclic group of sub-formula (bb) and Y is NR^4, and optionally when n^1 is 1, then R^4 is preferably not alkyl or substituted alkyl, i.e. or e.g. R^4 is preferably not C_{1-2}alkyl, C_{1-2}fluoroalkyl or $CH_2C(O)NH_2$. In one embodiment, when R^3 is the heterocyclic group of sub-formula (bb), Y is preferably O, S, SO_2 or NR^4, wherein R^4 is H, $C(O)NH_2$, C(O)-C_{1-2}alkyl or C(O)-C_1fluoroalkyl or more preferably Y is H or C(O)-Me. More preferably, for sub-formula (bb), Y is O or NR^4.

Preferably, NHR^3 or NR^3R^{3a} is of sub-formula (a), (a1), (b), (c), (c 1), (c 2), (c 3), (c 4), (c 5), (d), (e), (f), (g), (g1), (g2), (g3), (g4), (h), (h1), (i), (j), (k), (k1), (L), (m), (m1), (m2), (m3), (m5), (n), (o), (o1), (o2), (o3), (o4), (o5), (p), (p2), (p3), (p5), (p6), (p7), (p8), (q), (r), (s), (t), (t1) or (t2):


(a)
(a1)
(b)
(c)
(c 1)
(c 2)
(c 3)
(c 4)
(c 5)
(d)
(e)
(f)
(g)
(g1)
(g2)
(g3)
(g4)
(h)
(h1)
(i)
(j)
(k)
(k1)
(L)
(m)
(m 1)
(m 2)
(m 3)
(m 5)
(n)
(o)
(o1)
(o2)
(o3)
(o4)
(o5)
(p)
(p2)
(p3)
(p5)
(p6)
(p7)
(p8)
(q)
(r)
(s)
(t)
(t 1)
(t 2)

In the sub-formulae (a) to (t2) etc above, the -NH- connection point of the NHR^3 or NR^3R^{3a} group to the 4-position of the pyrazolopyridine of formula (I) is underlined. Generally, in this specification, for a group or radical, where NH or N are underlined, then this indicates the connection point.

Preferably, NHR^3 or NR^3R^{3a} is of sub-formula (c), (c 1), (c 2), (c 3), (c 4), (c 5), (d), (e), (f), (g1), (g4), (h), (h1), (i), (j), (k), (k1), (L), (m), (m1), (m2), (m3), (m5), (n), (o), (o1), (o2), (o3), (o4), (o5), (p), (p2), (p3), (p5), (p6), (p7), (q), (r), (s), (t), (t1) or (t2). More preferably, NHR^3 or NR^3R^{3a} is of sub-formula (c), (c1), (c 4), (c 5), (h), (i), (j), (k), (m1), (m2), (n), (o), (o2), (o3), (p2), (p5), (p6), (r), (s) or (t1). Still more preferably, NHR^3 or NR^3R^{3a} is of sub-formula (c), (h), (k), (n), (o), (o2) or (s); for example (c), (h), (o), (o2) or (s). Most preferably, R^3 is tetrahydro-2H-pyran-4-yl; that is NHR^3 or NR^3R^{3a} is most preferably of sub-formula (h), as shown above.

In one embodiment of the invention, NHR^3 or NR^3R^{3a} is of sub-formula (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (L), (m), (n), (o), (p), (q), (r), (s) or (t). In this embodiment, NHR^3 or NR^3R^{3a} is preferably of sub-formula (c), (h), (k), (n), (o), (r), (s) or (t), still more preferably (c), (h), (k), (n), (o) or (s).

In another embodiment of the invention, NHR^3 or NR^3R^{3a} is of sub-formula (a), (b), (c), (d), (e), (f), (g), (g1), (g2), (g3), (h), (i), (j), (k), (L), (m), (m1), (n), (o), (o1), (p), (q), (r), (s), (t), (t1) or (t2). In this embodiment, preferably, NHR^3 or NR^3R^{3a} is of sub-formula (c), (d), (e), (f), (h), (g1), (i), (j), (k), (m), (m1), (n), (o), (o1), (p), (q), (r), (s), (t), (t1) or (t2). More preferably NHR^3 or NR^3R^{3a} is of sub-formula (c), (h), (k), (n), (o), (r), (s), (t) or (t1), still more preferably (c), (h), (k), (n), (o), (s) or (t1). Most preferably, R^3 is tetrahydro-2H-pyran-4-yl; that is NHR^3 or NR^3R^{3a} is most preferably of sub-formula (h), shown above.

When NHR^3 or NR^3R^{3a} is of sub-formula (n), then preferably it is a *cis*-(3-hydroxycyclohex-1-yl)amino group, eg in any enantiomeric form or mixture of forms but it can be racemic.

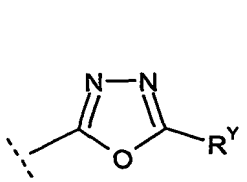
Preferably, Het is of sub-formula (i), (ii), (iii) or (v); more preferably Het is of sub-formula (i), (ii), or (v); still more preferably Het is of sub-formula (i).

X^1, X^3 and/or X^4 independently is/are often N (a nitrogen atom).

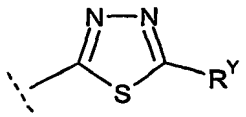
Y^1, Y^2 and/or Y^3 independently is/are often CR^Y.

Suitably, Z^1 and/or Z^5 independently is/are O or S. Preferably, Z^1 and/or Z^5 is O.

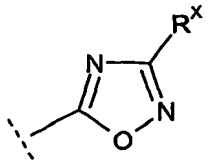
Preferably, Het is of sub-formula (ia), (ib), (ic), (id), (ie), (if) or (ig); more preferably of sub-formula (ia), (ib), (ic), (id), (if) or (ig) or of sub-formula (ia), (ib), (ic), (id), or (ie); still more preferably of sub-formula (ia), (ib), (ic), or (id); yet more preferably preferably of sub-formula (ia), (ic), or (id):



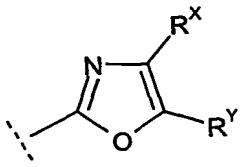
(ia)



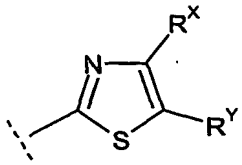
(ib)



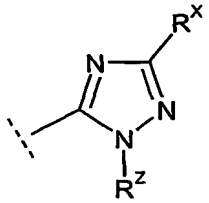
(ic)



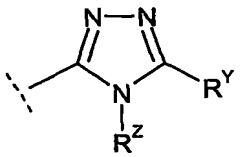
(id)



(ie)

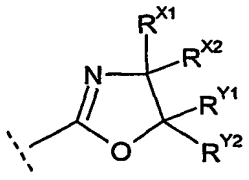


(i f)

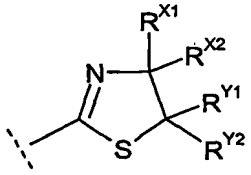


(ig)

Alternatively, when Het is of sub-formula (v), Het can for example be of sub-formula (va) or (vb), more preferably of sub-formula (va):

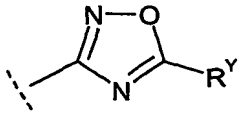


(va)



(vb)

Alternatively, when Het is of sub-formula (ii), Het can for example be of sub-formula (iia):



(iia)

Preferably, Het is of sub-formula (ia), (ib), (ic), (id), (if), (ig), (va) or (iia). More preferably, Het is of sub-formula (ia), (ic), (id) or (va).

For the Het group in general, R^W and/or R^Z independently is/are suitably a hydrogen atom (H).

For the Het group in general, preferably, one of R^X and R^Y (or R^{X2} and R^{Y2}) is as defined herein and the other of R^X and R^Y (or R^{X2} and R^{Y2}) is a hydrogen atom (H) or C_{1-2}alkyl. More preferably, one of R^X and R^Y (or R^{X2} and R^{Y2}) is as defined herein and the other of R^X and R^Y (or R^{X2} and R^{Y2}) is a hydrogen atom (H).

Overall, for the Het group in general, it is preferred that one of R^X and R^Y, and for Het of sub-formula (v) one of R^{X2} and R^{Y2}, is:

C_{1-8}alkyl;

optionally substituted C_{3-6}cycloalkyl;

$-(CH_2)_n{}^3-S(O)_2-R^5$, $-CH(C_{1-2}alkyl)-S(O)_2-R^5$, $-CMe_2-S(O)_2-R^5$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by $-S(O)_2-R^5$; preferably $-(CH_2)_n{}^3-S(O)_2-R^5$;

$-(CH_2)_n{}^4-NR^6R^7$, $-CH(C_{1-2}alkyl)-NR^6R^7$, $-CMe_2-NR^6R^7$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by $-NR^6R^7$; preferably $-(CH_2)_n{}^4-NR^6R^7$ or $-CH(Me)-NR^6R^7$;

$-(CH_2)_n{}^{11}-C(O)-NR^{10}R^{11}$, $-CH(C_{1-2}alkyl)-C(O)-NR^{10}R^{11}$, $-CMe_2-C(O)-NR^{10}R^{11}$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by $-C(O)-NR^{10}R^{11}$; preferably $-(CH_2)_n{}^{11}-C(O)-NR^{10}R^{11}$;

$-(CH_2)_n{}^{14}-Het^1$, $-CH(C_{1-2}alkyl)-Het^1$, $-CMe_2-Het^1$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by Het^1; preferably $-(CH_2)_n{}^{14}-Het^1$;

$-(CH_2)_n{}^{10}-Ar$, $-CH(C_{1-2}alkyl)-Ar$, $-CMe_2-Ar$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by Ar; preferably $-(CH_2)_n{}^{10}-Ar$;

(i) wherein Ar is optionally substituted phenyl, or more preferably (ii) wherein Ar is an optionally substituted 5- or 6-membered heterocyclic aromatic ring .

Overall, for the Het group in general, it is more preferred that one of R^X and R^Y, and for Het of sub-formula (v) one of R^{X2} and R^{Y2}, is:

$-(CH_2)_n{}^4-NR^6R^7$, $-CH(C_{1-2}alkyl)-NR^6R^7$, $-CMe_2-NR^6R^7$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by $-NR^6R^7$; preferably $-(CH_2)_n{}^4-NR^6R^7$ or $-CH(Me)-NR^6R^7$;

$-(CH_2)_n{}^{11}-C(O)-NR^{10}R^{11}$, $-CH(C_{1-2}alkyl)-C(O)-NR^{10}R^{11}$, $-CMe_2-C(O)-NR^{10}R^{11}$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by $-C(O)-NR^{10}R^{11}$; preferably $-(CH_2)_n{}^{11}-C(O)-NR^{10}R^{11}$;

$-(CH_2)_n{}^{14}-Het^1$, $-CH(C_{1-2}alkyl)-Het^1$, $-CMe_2-Het^1$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by Het^1; preferably $-(CH_2)_n{}^{14}-Het^1$; or

$-(CH_2)_n{}^{10}$-Ar, -CH(C_{1-2}alkyl)-Ar, -CMe_2-Ar, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by Ar; preferably $-(CH_2)_n{}^{10}$-Ar;

(i) wherein Ar is optionally substituted phenyl, or or more preferably (ii) wherein Ar is an optionally substituted 5- or 6-membered heterocyclic aromatic ring.

Optionally, one of R^X and R^Y can be: C_{1-8}alkyl; C_{3-6}cycloalkyl; $-(CH_2)_n{}^3$-SO_2-R^5; $-(CH_2)_n{}^4$-NR^6R^7; $-(CH_2)_n{}^7$-O-R^9; -C(O)-$NR^{10}R^{11}$; -C(O)-OR^{13}; or the 4-, 5-, 6- or 7-membered optionally substituted saturated heterocyclic ring Het^1. More preferably, one of R^X and R^Y is: C_{1-8}alkyl; $-(CH_2)_n{}^3$-SO_2-R^5; or the 4-, 5-, 6- or 7-membered optionally substituted saturated heterocyclic ring Het^1. In these cases, as mentioned above, it is preferred that the other of R^X and R^Y is a hydrogen atom (H) or C_{1-2}alkyl.

When R^X, R^{X2}, R^Y and/or R^{Y2} is C_{1-8}alkyl, then preferably it/they independently is/are C_{1-6}alkyl, e.g. C_{3-6}alkyl and/or C_{1-4}alkyl such as methyl, isopropyl, isobutyl or t-butyl.

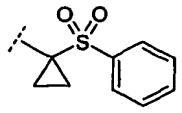
When R^X, R^{X2}, R^Y and/or R^{Y2} is optionally substituted C_{3-6}cycloalkyl, then optionally it/they independently can be C_{3-6}cycloalkyl optionally substituted by a C_{1-2}alkyl group.

When R^X, R^{X2}, R^Y and/or R^{Y2} is optionally substituted C_{3-6}cycloalkyl, then preferably it/they independently is/are C_{3-6}cycloalkyl (i.e. unsubstituted), for example cyclopropyl or cyclobutyl.

When R^X, R^{X2}, R^Y and/or R^{Y2} is optionally substituted $-(CH_2)_n{}^{2a}$-C_{3-6}cycloalkyl, then preferably it/they independently is/are $-(CH_2)_n{}^{2a}$-C_{3-6}cycloalkyl optionally substituted, in the $-(CH_2)_n{}^{2a}$- moiety or in the C_{3-6}cycloalkyl moiety, by a C_{1-2}alkyl group, wherein n^{2a} is 1, 2 or 3.

When R^X, R^{X2}, R^Y and/or R^{Y2} is optionally substituted $-(CH_2)_n{}^{2a}$-C_{3-6}cycloalkyl; then n^{2a} is preferably 1 or 2 or more preferably 1; and/or preferably R^X, R^{X2}, R^Y and/or R^{Y2} independently is/are optionally substituted $-(CH_2)_n{}^{2a}$-C_{5-6}cycloalkyl or optionally substituted $-(CH_2)_n{}^{2a}$-C_6cycloalkyl. When R^X, R^{X2}, R^Y and/or R^{Y2} is optionally substituted $-(CH_2)_n{}^{2a}$-C_{3-6}cycloalkyl, then preferably it/they independently is/are $-(CH_2)_n{}^{2a}$-C_{3-6}cycloalkyl (i.e. not substituted). More preferably R^X, R^{X2}, R^Y and/or R^{Y2} independently is/are (cyclohexyl)methyl-, that is $-CH_2$-cyclohexyl. When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^3$-$S(O)_2$-R^5, -CH(C_{1-2}alkyl)-$S(O)_2$-R^5 (e.g.

-CH(Me)-$S(O)_2$-R^5), -CMe_2-$S(O)_2$-R^5, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by -$S(O)_2$-R^5, then preferably it/they independently is/are -$(CH_2)_n{}^3$-$S(O)_2$-R^5.

When R^X, R^{X2}, R^Y and/or R^{Y2} is C_{3-5}cycloalkyl substituted at the connecting carbon atom by -$S(O)_2$-R^5, then preferably it/they independently is/are C_3cycloalkyl (cyclopropyl) substituted at the connecting carbon atom by -$S(O)_2$-R^5, for example  (see for example Example 178).

When R^X, R^{X2}, R^Y and/or R^{Y2} is -$(CH_2)_n{}^3$-$S(O)_2$-R^5, then preferably n^3 is 1.

Preferably, R^5 is C_{1-4}alkyl (e.g. C_{1-3}alkyl), -$NR^{15}R^{16}$, or optionally substituted phenyl. R^5 is more preferably C_{1-3}alkyl or -NH-C_{1-2}alkyl or phenyl; still more preferably R^5 is C_{1-3}alkyl or C_{1-2}alkyl such as methyl. Most preferably, -$(CH_2)_n{}^3$-$S(O)_2$-R^5 is -CH_2SO_2Me.

Preferably, R^{15} is H, C_{1-4}alkyl (e.g. C_{1-2}alkyl), optionally substituted phenyl or optionally substituted benzyl; and/or preferably R^{16} is H or methyl, e.g. H.

When R^{15} and R^{16} together are -$(CH_2)_n{}^{3a}$-X^{3a}-$(CH_2)_n{}^{3b}$-, then: preferably n^{3a} and/or n^{3b} independently are 2; and/or preferably X^{3a} is a bond, -CH_2-, O, or NR^{8a} wherein R^{8a} is C_{1-2}alkyl or acetyl; and/or preferably the ring formed by $NR^{15}R^{16}$ is not substituted on a ring carbon or is substituted on a ring carbon by one methyl or oxo (=O) substituent.

When R^X, R^{X2}, R^Y and/or R^{Y2} is -$(CH_2)_n{}^4$-NR^6R^7, -$CH(C_{1-2}alkyl)$-NR^6R^7 (e.g. -CH(Me)-NR^6R^7), -CMe_2-NR^6R^7, or C_{3-5}cycloalkyl (e.g. C_3cycloalkyl) substituted at the connecting carbon atom by -NR^6R^7, then preferably it/they independently is/are -$(CH_2)_n{}^4$-NR^6R^7, -$CH(C_{1-2}alkyl)$-NR^6R^7 (e.g. -CH(Me)-NR^6R^7), or -CMe_2-NR^6R^7; more preferably it/they independently is/are -CH(Me)-NR^6R^7 or still more preferably -$(CH_2)_n{}^4$-NR^6R^7.

When R^X, R^{X2}, R^Y and/or R^{Y2} is -$(CH_2)_n{}^4$-NR^6R^7, then preferably n^4 is 0 only when the -$(CH_2)_n{}^4$-NR^6R^7 is bonded to a carbon atom in the Het ring.

When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^4-NR^6R^7$, then preferably n^4 is 0, 1 or 2; more preferably n^4 is 0 or 1, still more preferably n^4 is 1.

In one optional embodiment of the invention, R^6 and R^7 independently are H, C_{1-6}alkyl e.g. C_{1-4}alkyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, $-C(O)-C_{1-2}$alkyl, $-SO_2-C_{1-2}$alkyl, phenyl, or benzyl (wherein the phenyl and benzyl are independently optionally substituted on the aromatic ring by one of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy); or R^6 and R^7 together are $-(CH_2)_n{}^5-X^5-(CH_2)_n{}^6-$ in which n^5 and n^6 independently are 2 or 3 and X^5 is a bond, $-CH_2-$, O, or NR^8 wherein R^8 is H or C_{1-2}alkyl, and wherein the ring formed by NR^6R^7 is not substituted on a ring carbon.

In one optional embodiment of the invention, R^6 and R^7 independently are H, C_{1-6}alkyl e.g. C_{1-4}alkyl, $-C(O)-C_{1-2}$alkyl or $-SO_2-C_{1-2}$alkyl; or R^6 and R^7 together are $-(CH_2)_n{}^5-X^5-(CH_2)_n{}^6-$ in which n^5 and n^6 independently are 2 or 3 and X^5 is a bond, $-CH_2-$, O, or NR^8 wherein R^8 is H or C_{1-2}alkyl, and wherein the ring formed by NR^6R^7 is not substituted on a ring carbon.

R^6 is preferably H or C_{1-6}alkyl. R^7 is preferably C_{1-6}alkyl, $-C(O)R^{17}$ or $-S(O)_2R^{18}$, for example C_{1-6}alkyl. Where R^6 and/or R^7 is C_{1-6}alkyl, then it/they independently is/are preferably C_{1-4}alkyl e.g. methyl.

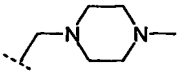
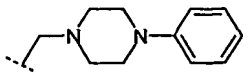
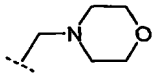
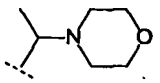
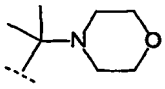
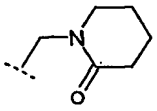
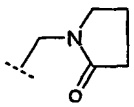
Preferably, R^{17} and R^{18} independently are C_{1-6}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl or isopropyl or n-propyl), C_{3-6}cycloalkyl, optionally substituted 5-membered heteroaryl being furyl (furanyl, e.g. 2-furyl) or thienyl (e.g. 2- or 3- thienyl) (the furyl or thienyl being independently optionally substituted by one oxo and/or one or two methyl), or phenyl or benzyl (wherein the phenyl and benzyl are independently optionally substituted on the aromatic ring by one or two substituents independently being fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy).

In an alternative preferable embodiment, R^6 and R^7 together are $-(CH_2)_n{}^5-X^5-(CH_2)_n{}^6-$, in which case it is preferable that n^5 is 2 and/or n^6 is 2. Preferably, when R^6 and R^7 together are $-(CH_2)_n{}^5-X^5-(CH_2)_n{}^6-$, and when the ring formed by NR^6R^7 is substituted on a ring carbon by one or two substituents being oxo (=O), then the one or two oxo substituents are substituted on a ring carbon atom adjacent to (bonded to) the connecting nitrogen N of NR^6R^7. When R^6 and R^7 together are $-(CH_2)_n{}^5-X^5-(CH_2)_n{}^6-$, then preferably the ring formed by NR^6R^7 is optionally substituted on a ring carbon by one or

two substituents independently being methyl or oxo (=O) only when X^5 is a bond or $-CH_2-$.

When R^6 and R^7 together are $-(CH_2)_n{}^5-X^5-(CH_2)_n{}^6-$, it is preferable that the ring formed by NR^6R^7 is not substituted on a ring carbon or is substituted on a ring carbon by one methyl or oxo (=O) substituent.

Preferably, R^8 is C_{1-2}alkyl or phenyl.

For example, $-(CH_2)_n{}^4-NR^6R^7$, $-CH(C_{1-2}alkyl)-NR^6R^7$ or $-CMe_2-NR^6R^7$ can be: $-CH_2-NHC(O)R^{17}$, $-CH_2-NMeC(O)R^{17}$, $-CH(Me)-NHC(O)R^{17}$, $-CH_2-NHS(O)_2R^{18}$, $-CH_2-NMeS(O)_2R^{18}$, $-CH(Me)-NHS(O)_2R^{18}$, NMe_2 ($n^4 = 0$; $R^6 = R^7 = Me$), or $-CH_2NMe_2$ ($n^4 = 1$; $R^6 = R^7 = Me$), or  ($n^4 = 1$; R^6 and R^7 together are $-(CH_2)_2-N(Me)-(CH_2)_2-$), or  , or  ($n^4 = 1$; R^6 and R^7 together are $-(CH_2)_2-O-(CH_2)_2-$), or  , or  , or  , or  .

When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^7-O-R^9$, then in one embodiment n^7 is 1, 2 or 3 and/or R^9 is H, C_{1-6}alkyl or phenyl, or more preferably R^9 is H or C_{1-6}alkyl. n^7 is preferably 1 or 2, more preferably 1. R^9 is preferably C_{1-4}alkyl such as methyl or t-butyl. For example, $-(CH_2)_n{}^7-O-R^9$ can be $-CH_2-O-{}^tBu$ or $-CH_2-O-Me$.

When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{11}-C(O)-NR^{10}R^{11}$, $-CH(C_{1-2}alkyl)-C(O)-NR^{10}R^{11}$ (e.g. $-CH(Me)-C(O)-NR^{10}R^{11}$), $-CMe_2-C(O)-NR^{10}R^{11}$, or C_{3-5}cycloalkyl (e.g. C_3cycloalkyl) substituted at the connecting carbon atom by $-C(O)-NR^{10}R^{11}$, then: preferably it/they independently is/are $-(CH_2)_n{}^{11}-C(O)-NR^{10}R^{11}$, $-CH(C_{1-2}alkyl)-C(O)-NR^{10}R^{11}$ (e.g. $-CH(Me)-C(O)-NR^{10}R^{11}$), or $-CMe_2-C(O)-NR^{10}R^{11}$; more preferably $-(CH_2)_n{}^{11}-C(O)-NR^{10}R^{11}$; still more preferably $-CH_2-C(O)-NR^{10}R^{11}$ or $-C(O)-NR^{10}R^{11}$.

When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{11}-C(O)-NR^{10}R^{11}$, then n^{11} is preferably 0 or 1, more preferably 1.

Preferably R^{10} is H or C_{1-6}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl or methyl), or R^{10} and R^{11} together are $-(CH_2)_n{}^8-X^6-(CH_2)_n{}^9-$.

Preferably, R^{10} and R^{11} independently are, and more preferably R^{11} is: H; C_{1-6}alkyl; C_{1-2}fluoroalkyl; C_{2-3}alkyl substituted by one OH or $-OC_{1-2}$alkyl other than at the connection point; C_{3-6}cycloalkyl optionally substituted by one or two methyl groups; $-CH_2-C_{3-6}$cycloalkyl optionally substituted by one NHMe group (preferably unsubstituted); $-(CH_2)_n{}^{17}$-Het^2; optionally substituted carbon-linked-pyridinyl, optionally substituted phenyl; optionally substituted benzyl; or optionally substituted $-CH(C_{1-2}alkyl)Ph$.

More, preferably, R^{10} and R^{11} independently are, and still more preferably R^{11} is: H; C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted by one or two methyl groups; $-CH_2-C_{3-6}$cycloalkyl (unsubstituted); $-(CH_2)_n{}^{17}$-Het^2; optionally substituted carbon-linked-pyridinyl; optionally substituted phenyl, optionally substituted benzyl; or optionally substituted $-CH(C_{1-2}alkyl)Ph$ (e.g. optionally substituted -CH(Me)Ph).

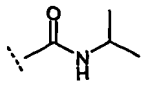
Preferably, in R^{10} and/or R^{11}, the phenyl, the benzyl and the $-CH(C_{1-2}alkyl)Ph$ (e.g. -CH(Me)Ph) are independently optionally substituted on the aromatic ring by one or two substituents independently being: fluoro, chloro, C_{1-2}alkyl (e.g. methyl), C_1fluoroalkyl (e.g. CF_3), C_{1-2}alkoxy (e.g. methoxy), C_1fluoroalkoxy (e.g. CF_3O- or CHF_2O-), $-NR^{10a}R^{10b}$ (wherein R^{10a} is H or methyl and R^{10b} is H, C_{1-2}alkyl (e.g. methyl), -C(O)Me or $-S(O)_2Me$), $-C(O)-NR^{10c}R^{10d}$ (wherein R^{10c} and R^{10d} independently are H or C_{1-2}alkyl, e.g. H or Me), or $-S(O)_2-R^{10e}$ (wherein R^{10e} is C_{1-2}alkyl (e.g. methyl), NH_2, NHMe or NMe_2). One substituent is preferred.

In R^{10} and/or R^{11}, and/or (independently) in R^5, and/or (independently) in R^{15}, and/or (independently) in R^6 and/or R^7, and/or (independently) in R^{17}, and/or (independently) in R^{18}: the carbon-linked-pyridinyl is preferably optionally substituted by one OH (including any keto tautomer thereof), and more preferably is not substituted.

In R^{10} and/or R^{11}, for $-(CH_2)_n{}^{17}$-Het^2, preferably n^{17} is 0 or 1; and/or preferably Het^2 is a 5- or 6- membered saturated optionally substituted heterocyclic ring containing one O or S (preferably O) ring atom or one NR^{27} ring group. Preferably, R^{27} is C_{1-2}alkyl or -C(O)Me. Preferably, the Het^2 ring is substituted on a ring carbon by one or two substituents being methyl or is not substituted on a ring carbon.

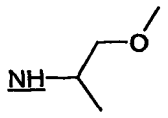
In one embodiment when R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{11}-C(O)-NR^{10}R^{11}$, $-CH(C_{1-2}alkyl)-C(O)-NR^{10}R^{11}$ or $-CMe_2-C(O)-NR^{10}R^{11}$, then optionally: R^{10} and R^{11} independently are H or C_{1-6}alkyl; or R^{10} and R^{11} together are $-(CH_2)_n{}^8-X^6-(CH_2)_n{}^9-$ in which n^8 and n^9 independently are 2 or 3 and X^6 is a bond, $-CH_2-$, O, or NR^{12} wherein R^{12} is H or C_{1-2}alkyl, and wherein the ring formed by $NR^{10}R^{11}$ is not substituted on a ring carbon.

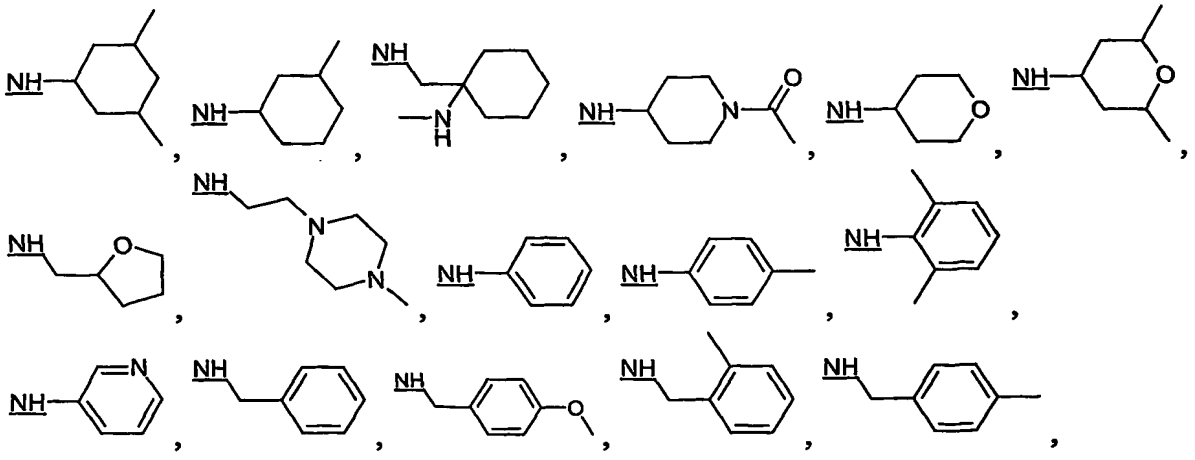
Preferably R^{10} is H and/or optionally R^{11} is C_{1-6}alkyl e.g. C_{1-4}alkyl such as isopropyl.

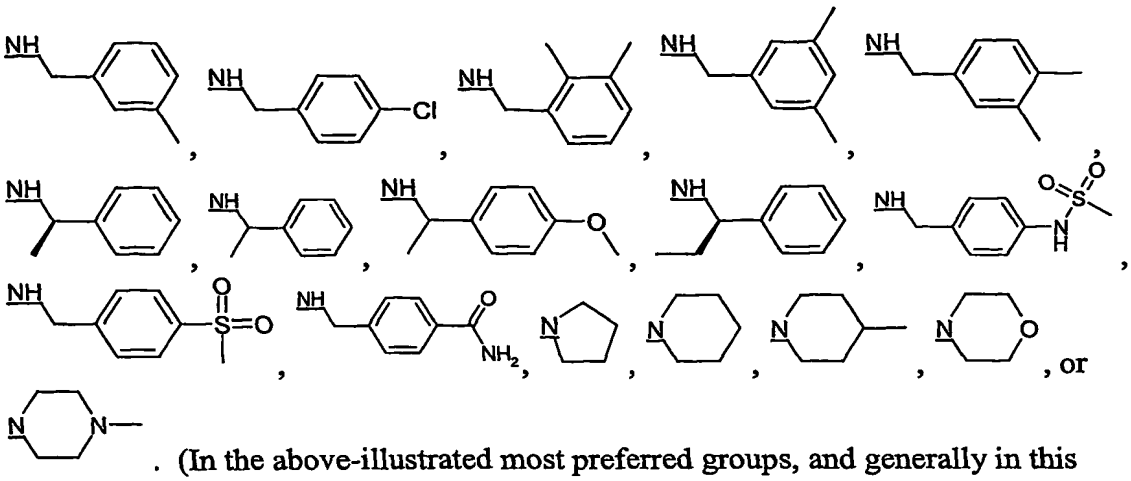
For example, $-(CH_2)_n{}^{11}-C(O)-NR^{10}R^{11}$ such as $-C(O)-NR^{10}R^{11}$ can be  .

In an alternative preferable embodiment, when R^{10} and R^{11} together are $-(CH_2)_n{}^8-X^6-(CH_2)_n{}^9-$, then preferably n^8 is 2 and/or n^9 is 2. When R^{10} and R^{11} together are $-(CH_2)_n{}^8-X^6-(CH_2)_n{}^9-$, which is a preferable feature of the invention, then preferably X^6 is a bond, $-CH_2-$, O, or NR^{12} wherein R^{12} is H or C_{1-2}alkyl, and wherein the ring formed by $NR^{10}R^{11}$ is not substituted on a ring carbon.

When R^{10} and R^{11} together are $-(CH_2)_n{}^8-X^6-(CH_2)_n{}^9-$, it is preferable that the ring formed by $NR^{10}R^{11}$ is not substituted on a ring carbon or is substituted on a ring carbon by one methyl or oxo (=O) substituent.

Most preferably, $NR^{10}R^{11}$ is: NH_2, NHMe, NMe_2, NHEt, NH^iPr,  ,





. (In the above-illustrated most preferred groups, and generally in this specification for a group or radical, where NH or N are underlined, then this indicates the connection point.)

Still more preferably, When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{11}$-C(O)-$NR^{10}R^{11}$, $-CH(C_{1-2}alkyl)$-C(O)-$NR^{10}R^{11}$, $-CMe_2$-C(O)-$NR^{10}R^{11}$, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by -C(O)-$NR^{10}R^{11}$, then preferably it/they independently is/are $-(CH_2)_n{}^{11}$-C(O)-$NR^{10}R^{11}$ (more preferably $-CH_2$-C(O)-$NR^{10}R^{11}$ or -C(O)-$NR^{10}R^{11}$) wherein $NR^{10}R^{11}$ is one of the above-illustrated most preferred $NR^{10}R^{11}$ groups.

The $-(CH_2)_n{}^{11}$-C(O)-$NR^{10}R^{11}$ group is preferably as defined in any of Examples 36, 58, 84, 85-90, 95-96, 126-147 or 148-155. These Examples illustrate some of the above-illustrated preferred $NR^{10}R^{11}$ groups, and some of these Examples give literature references and/or commercial sources for amines $R^{10}R^{11}NH$, which may be used to prepare the compounds of Formula (I) containing the $-(CH_2)_n{}^{11}$-C(O)-$NR^{10}R^{11}$ group as R^X, R^{X2}, R^Y and/or R^{Y2}.

When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{12}$-C(O)-OR^{13} , n^{12} is preferably 0 or 1, more preferably 1. In one preferred embodiment when R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{12}$-C(O)-OR^{13} , R^{13} is H or C_{1-6}alkyl. When R^{13} is C_{1-6}alkyl, then R^{13} is preferably C_{1-4}alkyl or C_{1-3}alkyl such as methyl (e.g. R^X, R^Y and/or R^{X2} can be $-CO_2Me$) or ethyl.

When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{13}$-C(O)-R^{13a}, n^{13} is preferably 0 or 1, more preferably 1. When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{13}$-C(O)-R^{13a}, then suitably R^{13a} is C_{1-6}alkyl, C_{1-2}fluoroalkyl, C_{3-6}cycloalkyl, $-CH_2$-C_{3-6}cycloalkyl, benzyl, or phenyl (wherein the phenyl and benzyl are independently optionally substituted on the aromatic ring by one or two of (independently) (e.g. one of) fluoro,

chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy). More preferably R^{13a} is C_{1-6}alkyl or C_{1-4}alkyl or C_{1-2}alkyl.

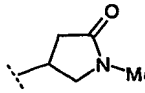
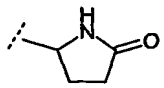
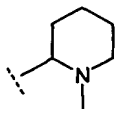
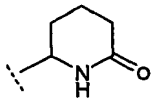
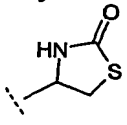
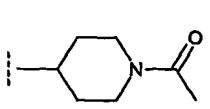
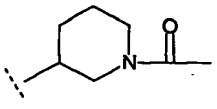
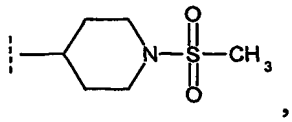
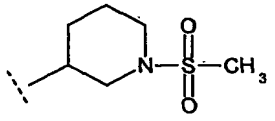
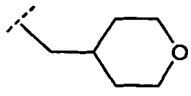
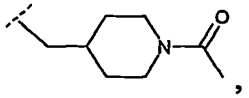
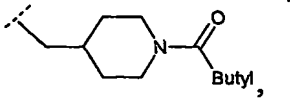
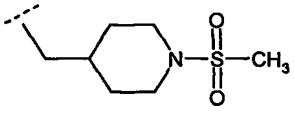
When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{14}$-Het^1, $-CH(C_{1-2}alkyl)$-Het^1 (e.g. $-CH(Me)$-Het^1), $-CMe_2$-Het^1, or C_{3-5}cycloalkyl (e.g. C_3cycloalkyl) substituted at the connecting carbon atom by Het^1, wherein n^{14} is 0, 1 or 2, then: (a) n^{14} is preferably 0 or 1, and/or (b) $-(CH_2)_n{}^{14}$-Het^1 is more preferred than $-CH(Me)$-Het^1 or $-CMe_2$-Het^1, or C_{3-5}cycloalkyl substituted at the connecting carbon atom by Ar.

When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{14}$-Het^1, $-CH(C_{1-2}alkyl)$-Het^1 (e.g. $-CH(Me)$-Het^1), $-CMe_2$-Het^1, or C_{3-5}cycloalkyl (e.g. C_3cycloalkyl) substituted at the connecting carbon atom by Het^1, wherein n^{14} is 0, 1 or 2 and wherein Het^1 is the 4-, 5-, 6- or 7-membered optionally substituted saturated heterocyclic ring containing one O or S ring atom and/or one NR^{14} ring group, then the optionally substituted saturated heterocyclic ring Het^1 is preferably 4-, 5- or 6-membered, more preferably preferably 5- or 6-membered. When Het^1 is 6-membered, then any O or S ring atom and/or any NR^{14} ring group independently can be present at the 2-, 3- or 4- ring position, preferably at the 4- ring position, with respect to the connecting ring-atom in Het^1. When the optionally substituted saturated heterocyclic ring Het^1 is 4-membered, then preferably the heterocyclic ring Het^1 is not optionally substituted by oxo (=O).

When R^{14} and/or a or the optional ring substituent is C_{1-4}alkyl, it is suitably C_{1-2}alkyl such as methyl. Preferably, R^{14} is C_{1-4}alkyl (e.g. C_{1-2}alkyl), $C(O)R^{19}$ or $S(O)_2R^{19}$. Preferably, R^{19} is C_{1-4}alkyl (e.g. methyl or isobutyl), C_{3-6}cycloalkyl such as cyclopropyl or cyclohexyl, 2-thienyl, furan-2-yl, phenyl (unsubstituted), or benzyl (unsubstituted); more preferably R^{19} is C_{1-4}alkyl (e.g. methyl or isobutyl).

When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{14}$-Het^1 and n^{14} is 0, and when the saturated heterocyclic ring Het^1 is optionally substituted (at a position other than any NR^{14} position) by C_{1-4}alkyl, then preferably the optional C_{1-4}alkyl is substituted at the carbon atom directly attached to the 5-membered ring in sub-formula (i), (ii), (iii), (iv) or (v) of Het.

The heterocyclic ring Het^1 is preferably optionally substituted (at a position or positions other than any NR^{14} position) by one oxo (=O) and/or one C_{1-4}alkyl substituent; preferably by one oxo (=O) substituent. Any oxo (=O) substituent is preferably substituted on a ring carbon adjacent to (bonded to) any NR^{14} ring group present. Preferably, in Het^1, the one or two oxo (=O) substituents are only present when there is a NR^{14} ring group present.

For example, when R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{14}$-Het^1, $-CH(C_{1-2}alkyl)$-Het^1, or $-CMe_2$-Het^1, the 4-, 5-, 6- or 7-membered optionally substituted saturated heterocyclic ring Het^1 can preferably be: tetrahydro-2*H*-pyranyl such as tetrahydro-2*H*-pyran-4-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or a positional isomer of any of the foregoing wherein the connection point [which connects to the $-(CH_2)_n{}^{14}$-, -CH(C1-2alkyl)- or $-CHMe_2$- or connecting-C_{3-5}cycloalkyl moiety or connects to the 5-membered ring of sub-formula (i), (ii), (iii), (iv) or (v) in Het] is at a different ring carbon atom of Het^1.

When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{10}$-Ar, $-CH(C_{1-2}alkyl)$-Ar (e.g. -CH(Me)-Ar), $-CMe_2$-Ar, or C_{3-5}cycloalkyl (e.g. C_3cycloalkyl) substituted at the connecting carbon atom by Ar, then preferably it/they independently is/are $-(CH_2)_n{}^{10}$-Ar or -CH(Me)-Ar, preferably $-(CH_2)_n{}^{10}$-Ar such as $-CH_2$-Ar.

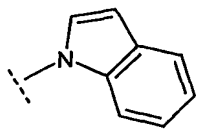
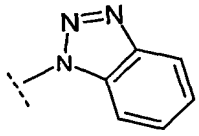
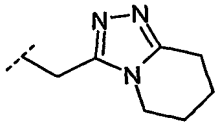
When R^X, R^{X2}, R^Y and/or R^{Y2} is $-(CH_2)_n{}^{10}$-Ar then preferably n^{10} is 0 or 1; more preferably n^{10} is 1.

When Ar is optionally substituted phenyl, preferably the phenyl is optionally substituted by one or two substituents (preferably one) independently being fluoro, chloro, bromo, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy, C_1fluoroalkoxy, $-NR^{11a}R^{11b}$ (wherein R^{11a} is H or methyl and R^{11b} is H, C_{1-2}alkyl, -C(O)Me or $-S(O)_2Me$), $-C(O)-NR^{11c}R^{11d}$ (wherein R^{11c} and R^{11d} independently are H or methyl), $-C(O)-OR^{11e}$ wherein R^{11e} is H, or $-S(O)_2-R^{11f}$ (wherein R^{11f} is methyl, NH_2, NHMe or NMe_2). When Ar is optionally substituted phenyl, more preferably $-(CH_2)_n{}^{10}$-Ar can be as defined for R^X, R^{X2}, R^Y and/or R^{Y2} in any of Examples 49-55, 83, 103, 107, 120-125, 179, 181-184, 189 or 190.

When Ar is phenyl optionally substituted at two adjacent Ar ring atoms by the two ends of a chain which is: $-(CH_2)_4-$, $-(CH_2)_3-$, or -CH=CH-CH=CH-, then it can be for example naphthyl e.g. 1-naphthyl or 2-naphthyl.

When Ar is the optionally substituted 5- or 6-membered heterocyclic aromatic ring containing 1, 2, 3 or 4 heteroatoms (e.g. 1, 2 or 3 heteroatoms) selected from O, N or S , then Ar can be optionally substituted: furyl, thienyl, pyrrolyl, 1,3-oxazolyl, 1,3-thiazolyl, imidazolyl, oxadiazolyl (e.g. 1,3,4- or 1,2,4- or 1,2,5- oxadiazolyl), thiadiazolyl (e.g. 1,3,4- or 1,2,4-), pyridyl, triazolyl (e.g. 1,2,3- or 1,2,4- triazolyl), tetrazolyl, triazinyl, pyridazyl, pyrimidinyl, pyrazolyl, isothiazolyl (1,2-thiazolyl), or isoxazolyl (1,2-oxazolyl). When Ar is the optionally substituted 5- or 6-membered heterocyclic aromatic ring, the ring is preferably optionally substituted by one or two independent C_{1-2}alkyl groups or by one OH group (including any keto tautomer thereof); more preferably the ring is optionally substituted by one or two independent C_{1-2}alkyl (e.g. methyl) groups; and still more preferably there is/are one or no substituents. When Ar is the optionally substituted 5- or 6-membered heterocyclic aromatic ring, preferably it is 5-membered.

When Ar is the 5- or 6-membered heterocyclic aromatic ring, more preferably $-(CH_2)_n{}^{10}$-Ar can be as defined for R^X, R^{X2}, R^Y and/or R^{Y2} in any of Examples 71, 79, 80, 97-100, 104-106, 108, 112-114, 117, 158 or 186.

When the heterocyclic aromatic ring Ar is substituted at two adjacent Ar ring atoms by the two ends of a chain which is: $-(CH_2)_4-$, $-(CH_2)_3-$, or -CH=CH-CH=CH-, then e.g. Ar can be  or  , or $-(CH_2)_n{}^{10}$-Ar can be  (see for example Example 186). Preferably, in these cases $-(CH_2)_n{}^{10}$-Ar is $-CH_2$-Ar.

In R^5, R^{15}, R^6, R^7, R^{17}, R^{18}, R^9, R^{13}, R^{13a}, and/or R^{19}, independent of each other, the phenyl and/or benzyl is/are preferably independently optionally substituted by one substituent; or more preferably the phenyl and/or benzyl is/are not substituted. In R^{10} and/or R^{11}, independent of each other, the phenyl, benzyl and/or $-CH(C_{1-2}alkyl)Ph$ is/are preferably independently optionally substituted by one substituent; or more preferably the the phenyl, benzyl and/or $-CH(C_{1-2}alkyl)Ph$ is/are not substituted. In Ar, the phenyl and/or the heterocyclic aromatic ring is/are preferably independently optionally substituted by one substituent; or more preferably the phenyl and/or the heterocyclic aromatic ring is/are not substituted. In Het^1 and/or Het^2, independent of each other, the saturated heterocyclic ring is/are preferably independently optionally substituted on a ring carbon by one substituent; or more preferably the saturated heterocyclic ring is/are not substituted on a ring carbon.

When Het is of sub-formula (v), then suitably R^{X2} and/or R^{Y2} independently is/are: a hydrogen atom (H), C_{1-6}alkyl (e.g. C_{1-4}alkyl such as methyl), C_{3-6}cycloalkyl, -C(O)-$NR^{10}R^{11}$, -C(O)-OR^{13}, or -$(CH_2)_n{}^{10}$-Ar; more preferably H, C_{1-6}alkyl, -C(O)-$NR^{10}R^{11}$, -C(O)-OR^{13}, or -$(CH_2)_n{}^{10}$-Ar; still more preferably H, C_{1-6}alkyl (e.g. C_{1-4}alkyl such as methyl), -C(O)-$NR^{10}R^{11}$, or -$(CH_2)_n{}^{10}$-Ar. In this instance, i.e. when Het is of sub-formula (v), then Ar is preferably optionally substituted phenyl and/or n^{10} is preferably 0 or 1..

Preferably, R^{X1} and/or R^{Y1} independently is/are a hydrogen atom (H) or C_{1-2}alkyl, more preferably H or methyl, still more preferably H.

Suitably, Y^5 can be CH_2 or CMe_2. More preferably, Y^5 is CH_2, i.e. $CR^{Y1}R^{Y2}$ wherein $R^{Y1} = R^{Y2}$ = a hydrogen atom (H).

X^5 can suitably be CHR^{X2} or CMe_2, for example CHMe, CH-CO_2Me or CMe_2.

It is particularly preferred that the compound of formula (I) or the salt thereof is:

N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-thiadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-N-(4-fluorophenyl)-5-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclopentyl-5-(1,3-dimethyl-1H-1,2,4-triazol-5-yl)-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclohexyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-N-isobutyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-N-isobutyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclohexyl-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,

N-[(1R)-1,2-dimethylpropyl]-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-[(1S)-1,2-dimethylpropyl]-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-cyclohexyl-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-isobutyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-[(1S)-1,2-dimethylpropyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-[(1R)-1,2-dimethylpropyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclohexyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-N-isobutyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-[(1S)-1,2-dimethylpropyl]-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-[(1R)-1,2-dimethylpropyl]-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-{3-[(Dimethylamino)methyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Cyclopropyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-{5-[(4-methylpiperazin-1-yl)methyl]-1,3,4-oxadiazol-2-yl}-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-isopropyl-1,3,4-oxadiazole-2-carboxamide,
4-{5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}-1-methylpyrrolidin-2-one,

1-Ethyl-N-tetrahydro-2H-pyran-4-yl-5-(5-tetrahydro-2H-pyran-4-yl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[5-(morpholin-4-ylmethyl)-1,3,4-oxadiazol-2-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-[5-(Tert-butoxymethyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine, or
methyl 2-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3-oxazole-4-carboxylate;

or a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

Alternatively, the compound of formula (I) or the salt thereof can preferably be:

Methyl 2-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-4,5-dihydro-1,3-oxazole-4-carboxylate,
1-Ethyl-5-(4-methyl-4,5-dihydro-1,3-oxazol-2-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-(n-Propyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-(5-methyl-1,2,4-triazol-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine, or
N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine;

or a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

Alternatively, the compound of formula (I) or the salt thereof can preferably be:

1-Ethyl-5-[(4R)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[(4S)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[(4S)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[(4R)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,

1-Ethyl-5-[(4S,5R)-5-methyl-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[(5R)-5-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[(5S)-5-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxylic acid,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-(1-methylethyl)-1,3-oxazole-4-carboxamide,
1-Ethyl-5-[4-(4-morpholinylcarbonyl)-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-N-methyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
trans-4-{[1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl]amino}cyclohexanol,
1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(tetrahydro-2H-pyran-3-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
4-{[1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl]amino}cyclohexanone,
1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-n-propyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-[5-(1,1-Dimethylethyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-6-methyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-6-methyl-N-(tetrahydro-2H-pyran-4-yl)-5-[5-(tetrahydro-2H-pyran-4-yl)-1,3,4-oxadiazol-2-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-(5-Cyclobutyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-{5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}-2-pyrrolidinone,
N-({5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}methyl)acetamide,
1-Ethyl-5-[5-(1-methyl-2-piperidinyl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-{5-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-1,3,4-oxadiazol-2-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
3-{5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}cyclopentanone,
1-Ethyl-5-[5-(tetrahydro-3-furanyl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,

(4S)-4-{5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}-1,3-thiazolidin-2-one,
5-[5-(2,2-Dimethylcyclopropyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-({5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}methyl)-N-methylacetamide,
1-Ethyl-N-(tetrahydro-2H-pyran-4-yl)-5-[5-(tetrahydro-2H-pyran-4-ylmethyl)-1,3,4-oxadiazol-2-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[5-(1-methylcyclobutyl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[5-(3-methyl-5-isoxazolyl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[5-(1-methyl-1H-pyrazol-5-yl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
5-[5-(1-Acetyl-4-piperidinyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-{3-[(4-methyl-1-piperazinyl)methyl]-1,2,4-oxadiazol-5-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine, or
1-Ethyl-5-{3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1,2,4-oxadiazol-5-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine;

or a salt thereof, e.g. a pharmaceutically acceptable salt thereof. For these compounds / salts, the structures of each, as a compound, are disclosed in Examples 49 to 84 hereinafter.

Alternatively, the compound of formula (I) or the salt thereof can preferably be:

2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-phenylacetamide,
2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-(1-phenylethyl)acetamide,
1-Ethyl-5-{3-[2-oxo-2-(1-piperidinyl)ethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-(phenylmethyl)acetamide,
2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*,*N*-dimethylacetamide,
N-Ethyl-2-{5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}acetamide,
1-Ethyl-5-{3-[1-(4-morpholinyl)ethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,

5-[3-(Cyclohexylmethyl)-1,2,4-oxadiazol-5-yl]-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-{3-[2-oxo-2-(1-piperidinyl)ethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-ethyl-5-{3-[2-(4-methyl-1-piperazinyl)-2-oxoethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-5-[5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3,4-oxadiazol-2-yl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
5-{5-[(2,4-Dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-[5-(2-furanylmethyl)-1,3,4-oxadiazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-[5-(3-isoxazolylmethyl)-1,3,4-oxadiazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-ethyl-5-(5-{[4-(methyloxy)phenyl]methyl}-1,3,4-oxadiazol-2-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-5-[5-(1*H*-tetrazol-1-ylmethyl)-1,3,4-oxadiazol-2-yl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-[5-(5-isothiazolylmethyl)-1,3,4-oxadiazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-{5-[(3-methyl-5-isoxazolyl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
5-(5-{[4-(Dimethylamino)phenyl]methyl}-1,3,4-oxadiazol-2-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine (1:1),
1-Ethyl-5-{5-[(2-methyl-1,3-thiazol-4-yl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
2-[1-({5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}methyl)cyclopentyl]-*N*-methylacetamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}methyl)cyclopropanecarboxamide,
1-Ethyl-5-{5-[(5-methyl-3-isoxazolyl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-{5-[(5-methyl-3-isoxazolyl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-{5-[2-(4-methyl-1,3-thiazol-5-yl)ethyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
5-{5-[(3,5-Dimethyl-4-isoxazolyl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
N-(1-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}ethyl)acetamide,
5-{5-[(1-acetyl-4-piperidinyl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,

1-Ethyl-5-{5-[(4-methylphenyl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
5-[5-(3,4-Dimethylphenyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
5-[5-(2,4-Dimethylphenyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
5-{5-[(4-Bromophenyl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
2-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-*N*-(phenylmethyl)-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-{[4-(methyloxy)phenyl]methyl}-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-[(2-methylphenyl)methyl]-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-[(4-methylphenyl)methyl]-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-[(3-methylphenyl)methyl]-1,3-oxazole-4-carboxamide,
N-[(4-Chlorophenyl)methyl]-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide,
N-[(2,3-Dimethylphenyl)methyl]-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide,
N-[(3,5-Dimethylphenyl)methyl]-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide,
N-[(3,4-Dimethylphenyl)methyl]-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-(1-phenylethyl)-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-{(1R)-1-[4-(methyloxy)phenyl]ethyl}-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-[(1R)-1-phenylpropyl]-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-(4-methylphenyl)-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-({4-[(methylsulfonyl)amino]phenyl}methyl)-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-{[4-(methylsulfonyl)phenyl]methyl}-1,3-oxazole-4-carboxamide,
N-(1-Acetyl-4-piperidinyl)-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide,

2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-(tetrahydro-2H-pyran-4-yl)-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-(tetrahydro-2-furanylmethyl)-1,3-oxazole-4-carboxamide,
2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-[2-(4-methyl-1-piperazinyl)ethyl]-1,3-oxazole-4-carboxamide,
N-[1-(Aminomethyl)cyclohexyl]-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-1,3-oxazole-4-carboxamide,
N-(2,6-Dimethylphenyl)-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide,
N-{[4-(Aminocarbonyl)phenyl]methyl}-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide,
2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)acetamide,
5-{3-[2-(2,6-Dimethyl-4-morpholinyl)-2-oxoethyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-{3-[2-(4-methyl-1-piperidinyl)-2-oxoethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-[1-methyl-2-(methyloxy)ethyl]acetamide,
5-{3-[2-(3,5-Dimethyl-1-piperidinyl)-2-oxoethyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-{3-[2-(3-methyl-1-piperidinyl)-2-oxoethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-3-pyridinylacetamide,
6-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}-2-piperidinone,
1-Ethyl-5-{5-[(3-methyl-1*H*-1,2,4-triazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)acetamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)benzamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-phenylacetamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-methylpropanamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-3-methylbutanamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)cyclohexanecarboxamide,

N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-furancarboxamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)methanesulfonamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)benzenesulfonamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-1-phenylmethanesulfonamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-propanesulfonamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-1-propanesulfonamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)cyclopropanesulfonamide,
N-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-thiophenesulfonamide,
1-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-pyrrolidinone,
1-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-piperidinone,
5-{3-[(1-Acetyl-4-piperidinyl)methyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-(3-{[1-(3-methylbutanoyl)-4-piperidinyl]methyl}-1,2,4-oxadiazol-5-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-(3-{[1-(methylsulfonyl)-4-piperidinyl]methyl}-1,2,4-oxadiazol-5-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-{3-[1-(phenylsulfonyl)cyclopropyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-[3-(1-phenylethyl)-1,2,4-oxadiazol-5-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-(3-{[4-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
5-(3-{[4-(Dimethylamino)phenyl]methyl}-1,2,4-oxadiazol-5-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
5-(3-{[3-(Dimethylamino)phenyl]methyl}-1,2,4-oxadiazol-5-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
5-(3-{[4-(Dimethylamino)phenyl]methyl}-1,2,4-oxadiazol-5-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-{3-[(phenyloxy)methyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,

1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-5-[3-(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridin-3-ylmethyl)-1,2,4-oxadiazol-5-yl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-{3-[(4-phenyl-1-piperazinyl)methyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-(5-ethyl-1,2,4-oxadiazol-3-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
5-(5-{[4-(Dimethylamino)phenyl]methyl}-1,2,4-oxadiazol-3-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-5-(5-{[4-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine, or
5-(3,8-Dioxa-1-azaspiro[4.5]dec-1-en-2-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine;

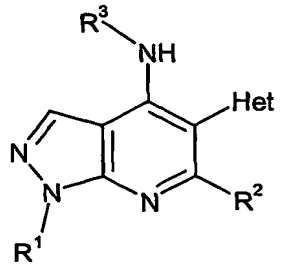
or a salt thereof, e.g. a pharmaceutically acceptable salt thereof. The structures of each of the above-listed compounds are disclosed in Examples 85 to 191 hereinafter.

Preferably, the compound of formula (I) or the salt thereof is:

1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine (the compound of Example 14),
5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine (the compound of Example 17),
1-Ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine (the compound of Example 23),
1-Ethyl-5-[5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine (the compound of Example 34),
1-Ethyl-5-{5-[(4-methylpiperazin-1-yl)methyl]-1,3,4-oxadiazol-2-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine (the compound of Example 35),
1-Ethyl-N-(tetrahydro-2H-pyran-4-yl)-5-[5-(tetrahydro-2H-pyran-4-yl)-1,3,4-oxadiazol-2-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine (the compound of Example 38),
also named: 1-Ethyl-5-[5-(morpholin-4-ylmethyl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine (the compound of Example 39),
1-Ethyl-5-[5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine (the compound of Example 44),
1-Ethyl-N-(tetrahydro-2H-pyran-4-yl)-5-[5-(tetrahydro-2H-pyran-4-ylmethyl)-1,3,4-oxadiazol-2-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine (the compound of Example 77), or
1-Ethyl-5-{3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1,2,4-oxadiazol-5-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine (the compound of Example 84);

or a salt thereof.

A second aspect of the present invention provides a compound of formula (IA) or a salt thereof (in particular, a pharmaceutically acceptable salt thereof):



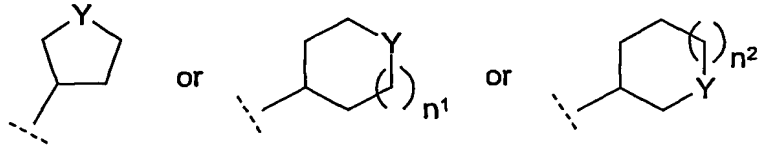
(IA)

wherein:

R^1 is C_{1-4}alkyl, C_{1-3}fluoroalkyl or $-(CH_2)_2OH$;

R^2 is a hydrogen atom (H), methyl or C_1fluoroalkyl;

R^3 is optionally substituted branched C_{3-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted phenyl, or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc):



(aa) (bb) (cc)

in which n^1 and n^2 independently are 1 or 2; and Y is O, S, SO_2, or NR^4; where R^4 is a hydrogen atom (H), C_{1-2}alkyl, C_{1-2}fluoroalkyl, $CH_2C(O)NH_2$, $C(O)NH_2$, $C(O)$-C_{1-2}alkyl, or $C(O)$-C_1fluoroalkyl;

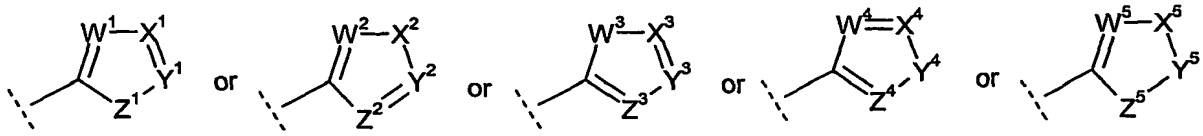
wherein in R^3 the optionally substituted branched C_{3-6}alkyl is optionally substituted with one or two substituents being oxo (=O), OH, C_{1-2}alkoxy or C_{1-2}fluoroalkoxy; and wherein any such substituent is not substituted at the R^3 carbon atom attached (bonded) to the -NH- group of formula (IA);

wherein in R^3 the phenyl is optionally substituted with one substituent being fluoro, chloro, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy or cyano;

wherein in R^3 the C_{3-8}cycloalkyl or the heterocyclic group of sub-formula (aa), (bb) or (cc) is optionally substituted with one or two substituents being oxo (=O), OH, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy, or C_{1-2}alkyl; and wherein any OH, alkoxy or

fluoroalkoxy substituent is not substituted at the R^3 ring carbon attached (bonded) to the -NH- group of formula (IA) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc);

and wherein Het is of sub-formula (i), (ii), (iii), (iv) or (v):



(i) (ii) (iii) (iv) (v)

wherein:
W^1, W^2, W^4 and W^5 is N; and W^3 is NR^W ;

X^1, X^3 and X^4 is N or CR^X; X^2 is O, S or NR^X ; and X^5 is $CR^{X1}R^{X2}$;

Y^1, Y^2 and Y^3 is CR^Y or N; Y^4 is O, S or NR^Y ; and Y^5 is $CR^{Y1}R^{Y2}$;

Z^1 and Z^5 is O, S or NR^Z; and Z^2, Z^3 and Z^4 is N or CR^Z;

wherein:
R^W is a hydrogen atom (H) or C_{1-2}alkyl;

R^X, R^{X2}, R^Y and R^{Y2} independently are:
a hydrogen atom (H);
C_{1-8}alkyl;
C_{3-6}cycloalkyl optionally substituted by a C_{1-2}alkyl group;
$-(CH_2)_n{}^{2a}$-C_{3-6}cycloalkyl optionally substituted, in the $-(CH_2)_n{}^{2a}$- moiety or in the C_{3-6}cycloalkyl moiety, by a C_{1-2}alkyl group, wherein n^{2a} is 1, 2 or 3;
$-(CH_2)_n{}^3$-SO_2-R^5 wherein n^3 is 1 or 2 and R^5 is C_{1-3}alkyl or -NH-C_{1-2}alkyl or phenyl;
$-(CH_2)_n{}^4$-NR^6R^7 wherein n^4 is 0, 1, 2 or 3, and R^6 and R^7 independently are H, C_{1-6}alkyl e.g. C_{1-4}alkyl, C_{3-6}cycloalkyl, $-CH_2$-C_{3-6}cycloalkyl, -C(O)-C_{1-2}alkyl, $-SO_2$-C_{1-2}alkyl, phenyl, or benzyl (wherein the phenyl or benzyl are independently optionally substituted on the aromatic ring by one of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy); or
R^6 and R^7 together are $-(CH_2)_n{}^5$-X^5-$(CH_2)_n{}^6$- in which n^5 and n^6

independently are 2 or 3 and X^5 is a bond, $-CH_2-$, O, or NR^8 wherein R^8 is H or C_{1-2}alkyl;

$-(CH_2)_n{}^7-O-R^9$; wherein n^7 is 0, 1, 2 or 3 and R^9 is H or C_{1-6}alkyl; wherein n^7 is 0 only when the $-(CH_2)_n{}^7-O-R^9$ is bonded to a carbon atom in the Het ring; and wherein n^7 is not 0 when Het is of sub-formula (v) (i.e. n^7 is not 0 for R^{X2} and for R^{Y2});

$-C(O)-NR^{10}R^{11}$ wherein R^{10} and R^{11} independently are H, C_{1-6}alkyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, phenyl, or benzyl (wherein the phenyl or benzyl are independently optionally substituted on the aromatic ring by one of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy); or R^{10} and R^{11} together are $-(CH_2)_n{}^8-X^6-(CH_2)_n{}^9-$ in which n^8 and n^9 independently are 2 or 3 and X^6 is a bond, $-CH_2-$, O, or NR^{12} wherein R^{12} is H or C_{1-2}alkyl;

$-C(O)-OR^{13}$ wherein R^{13} is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, phenyl, or benzyl (wherein the phenyl or benzyl are independently optionally substituted on the aromatic ring by one of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy);

$-C(O)-R^{13a}$ wherein R^{13a} is a hydrogen atom (H), C_{1-6}alkyl, C_{1-2}fluoroalkyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, benzyl, or phenyl; wherein the phenyl or benzyl are independently optionally substituted on the aromatic ring by one of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

a 4-, 5-, 6- or 7-membered saturated heterocyclic ring containing one O ring atom or one NR^{14} ring group wherein R^{14} is H or C_{1-4}alkyl, said heterocyclic ring being optionally substituted (at a position or positions other than any NR^{14} position) by one oxo (=O) and/or one C_{1-4}alkyl substituent; or

$-(CH_2)_n{}^{10}-Ar$ wherein n^{10} is 0, 1 or 2 and

(i) Ar is phenyl optionally substituted by one or two substituents being fluoro, chloro, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy or cyano; or

(ii) Ar is an optionally substituted 5- or 6-membered heterocyclic aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N or S; and wherein when the heterocyclic aromatic ring Ar contains 2 or 3 heteroatoms, one is selected from O, N and S and the remaining heteroatom(s) are N; and wherein the heterocyclic aromatic ring Ar is optionally substituted by one or two C_{1-4}alkyl groups;

R^{X1} and R^{Y1} independently are a hydrogen atom (H), C_{1-2}alkyl or C_1fluoroalkyl; and

R^Z is a hydrogen atom (H) or C_{1-2}alkyl.

Preferably, in formula (IA), when R^3 is the heterocyclic group of sub-formula (bb), n^1 is 1, and Y is NR^4, then R^4 is not C_{1-2}alkyl, C_{1-2}fluoroalkyl or $CH_2C(O)NH_2$.

Examples 1-48 are examples of compounds or salts of the second aspect of the invention (Formula (IA)).

The preferred or optional features for the compound of formula (IA) or salt thereof are the same as or similar to the preferred or optional features for the compound or salt of formula (I), with all necessary changes (for example to the formula, to the R groups and/or to substituents) having been made. Generally, whenever formula (I) is mentioned herein, then in alternative embodiments the statement mentioning formula (I) applies to formula (IA), with all necessary changes having been made.

Salts, solvates, isomers, tautomeric forms, molecular weights, etc.

Because of their potential use in medicine, the salts of the compounds of formula (I) are preferably pharmaceutically acceptable. Suitable pharmaceutically acceptable salts can include acid or base addition salts.

A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, formic, acetic, propionic, fumaric, citric, tartaric, lactic, benzoic, salicylic, glutamaic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, formate, acetate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2- naphthalenesulfonate) or hexanoate salt. In one embodiment, the pharmaceutically acceptable acid addition salt can be a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, acetate, fumarate, citrate, tartrate, benzoate, p-toluenesulfonate, methanesulfonate or naphthalenesulfonate salt.

A pharmaceutically acceptable base addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic base (e.g. triethylamine, ethanolamine, triethanolamine, choline, arginine, lysine or histidine), optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration.

Other suitable pharmaceutically acceptable salts include pharmaceutically acceptable metal salts, for example pharmaceutically acceptable alkali-metal or alkaline-earth-metal salts such as sodium, potassium, calcium or magnesium salts; in particular pharmaceutically acceptable metal salts of one or more carboxylic acid moieties that may be present in the the compound of formula (I).

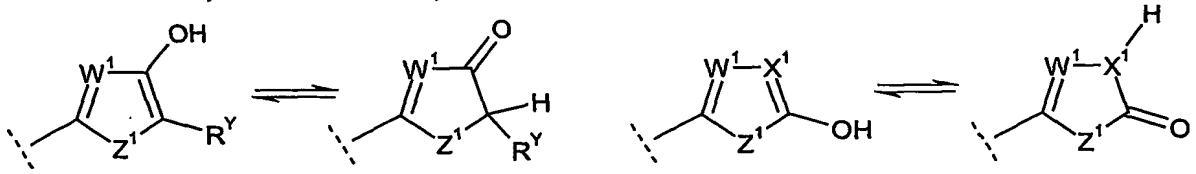
Other non-pharmaceutically acceptable salts, eg. oxalates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I).

Also included within the scope of the invention are all solvates, hydrates and complexes of compounds and salts of the invention.

Certain groups, substituents, compounds or salts included in the present invention may be present as isomers. The present invention includes within its scope all such isomers, including racemates, enantiomers and mixtures thereof.

Certain of the groups, e.g. heteroaromatic ring systems, included in compounds of formula (I) or their salts may exist in one or more tautomeric forms. The present invention includes within its scope all such tautomeric forms, including mixtures. For example, when Het is of sub-formula (i), Y^1 is CR^Y, and X^1 is CR^X wherein R^X is OH, then the compounds of formula (I) or their salts include the keto form (K1), the enol form (E1), and mixtures thereof, as shown below, unless otherwise indicated; and when Het is of sub-formula (i) and Y^1 is CR^Y wherein R^Y is OH, then the compounds of formula (I) or their salts include the keto form (K2), the enol or hydroxy-imine form (E2), and mixtures thereof, as shown below, unless otherwise indicated:



E1 K1 E2 K2

Especially when intended for oral medicinal use, the compound of formula (I) can optionally have a molecular weight of 1000 or less, for example 800 or less, in particular 650 or less or 600 or less. Molecular weight here refers to that of the unsolvated "free base" compound, that is excluding any molecular weight contributed by any addition salts, solvent (e.g. water) molecules, etc.

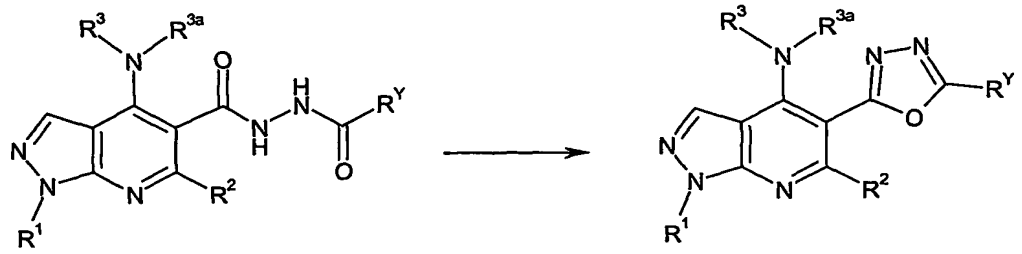
Synthetic Process Routes

The following processes can be used to make the compounds of formula (I). The methods are sometimes illustrated for the circumstance where R^2 is H or Me. However,

some or all of these processes are thought to be usable with appropriate modification, e.g. of starting materials and reagents, for making compounds of Formula (I) wherein R^2 is C_1fluoroalkyl.

Process A

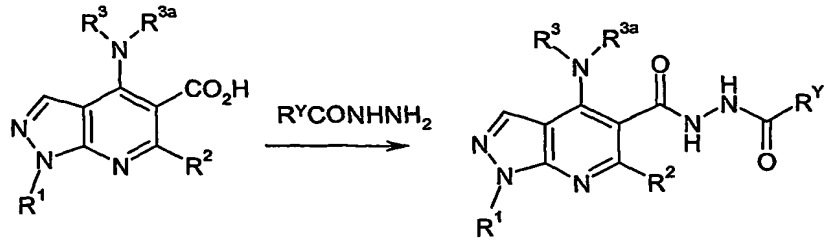
Compounds of formula (I) which are compounds of Formula I(ia) (that is, compounds of formula (I) wherein Het is of sub-formula (ia)) can be prepared by the cyclisation reaction of a compound of Formula II, for example in the presence of a dehydrating agent such as phosphorous oxychloride ($POCl_3$) or Burgess reagent [(Methoxycarbonylsulphamoyl)triethylammonium hydroxide], and/or preferably in a suitable solvent (e.g. organic solvent, preferably anhydrous) such as acetonitrile (e.g. for $POCl_3$) or THF and/or DMF (e.g. for Burgess reagent). The reaction may require heating, for example heating to from about 70 to about 150 °C or heating to from about 70 to about 120 °C or heating to from about 70 to about 90 °C:



Formula II Formula I(ia)

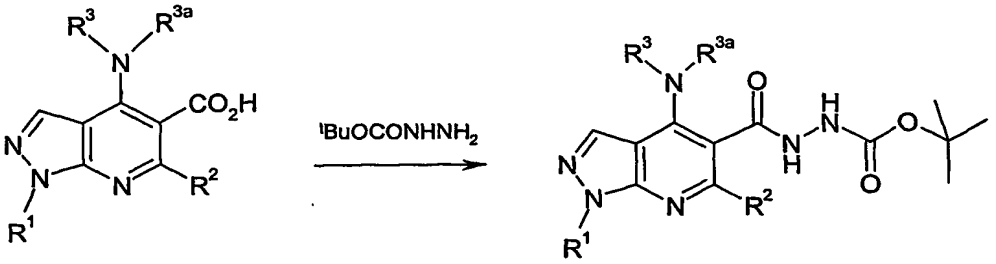
For the Formula II to Formula I(ia) cyclisation reaction, the conditions can for example be as described in (a) Examples 1-3 or 43 ($POCl_3$ and acetonitrile), or (b) in Examples 32, 34-37, 35 (alternative synthesis), 38-40, 44, 66 or 97-125 (Burgess reagent, with THF and/or DMF).

Compounds of Formula II may themselves be prepared by reacting a compound of Formula III with a suitably substituted hydrazine derivative of formula $R^YCONHNH_2$, under standard coupling conditions. For example a coupling reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) may be used e.g. in the presence of hydroxybenzotriazole (HOBT) , for example in a suitable solvent such as DMF:



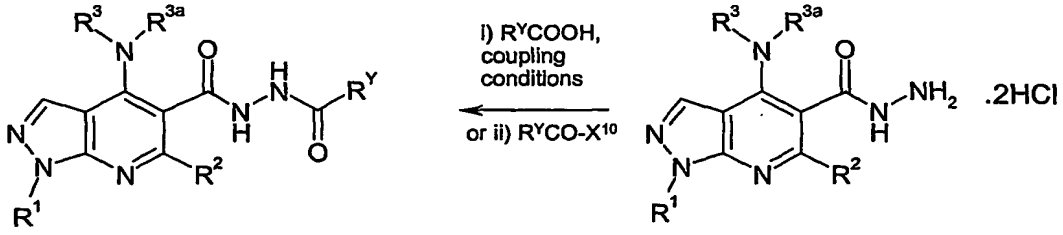
Formula III Formula II

Where the required hydrazine derivative $R^YCONHNH_2$ is not readily available, compounds of Formula II may alternatively be prepared by initially reacting a compound of Formula III with a carbazate $ROCONHNH_2$ such as t-butylcarbazate $^tBuOCONHNH_2$ under coupling conditions to form a compound of formula IV. For example a coupling reagent such as EDC may be used, e.g. in the presence of hydroxybenzotriazole, for example in a suitable solvent such as DMF:



Formula III Formula IV

Boc deprotection



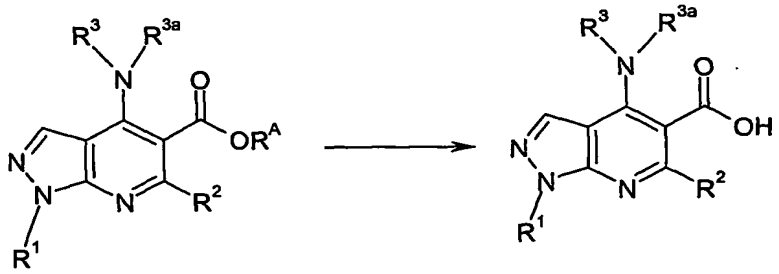
Formula II Formula V

Subsequent Boc-deprotection of the resultant acid hydrazide derivative (compound of Formula IV) to afford a hydrazide derivative of Formula V, can be achieved using a dilute acid such as 2M hydrochloric acid in an organic solvent such as dioxane.

The compound of Formula V can be converted to the compound of Formula II (the desired hydrazide derivative). This can be achieved by reaction of the compound of Formula V with an acid of formula R^YCO_2H under coupling conditions. For example a coupling agent such as EDC may be used e.g. in the presence of hydroxybenzotriazole

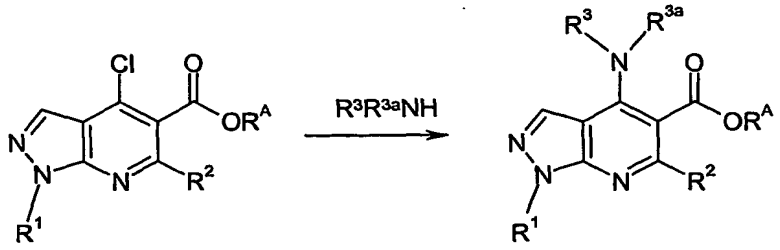
(HOBT), for example in a suitable solvent such as DMF. Alternatively, an activated acid derivative of formula $R^YCO\text{-}X^{10}$ where X is a leaving group such as chloro (acid chloride) or $-O\text{-}CO\text{-}R^{30}$ or $-O\text{-}SO_2\text{-}R^{30}$ (where R^{30} can e.g. be R^Y or alkyl or aryl such as methyl, t-butyl or p-methylphenyl) may be used to effect formation of a hydrazide of Formula II, through reaction with a hydrazide derivative of Formula V.

Compounds of Formula III can be prepared by hydrolysis of an ester of Formula VI (for example R^A can be C_{1-6}alkyl such as Et), for example according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027. This hydrolysis procedure usually involves reaction with a base such as sodium hydroxide or potassium hydroxide in a solvent such as ethanol or dioxane (e.g. NaOH in EtOH), one or both solvents preferably containing some water:



Formula VI Formula III

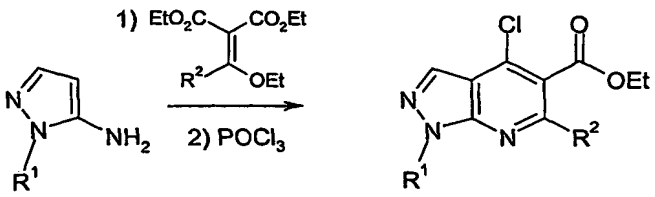
Compounds of Formula VI can be prepared, e.g. according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027, by reaction of a compound of Formula VII with an amine of Formula $R^3R^{3a}NH$. The reaction is best carried out in the presence of a base such as triethylamine or diisopropylethyl amine in a solvent such as ethanol or dioxane (e.g. NEt_3 in EtOH) and may require heating:



Formula VII Formula VI

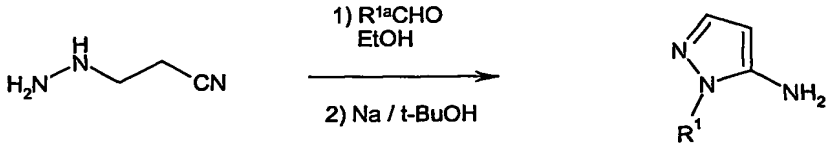
Many amines of Formula $R^3R^{3a}NH$, e.g. those amines wherein $R^3R^{3a}N$ are of sub-formulae (a) to (t2), are either commercially available, or syntheses therefor have been published and/or described herein, or they can be prepared from commercially available or synthesizable compounds e.g. from other amines of Formula $R^3R^{3a}NH$ or derivatives thereof. For amines $R^3R^{3a}NH$ whose preparations and/or specific commercial sources are described herein, see e.g. Intermediates 21, 21A, 25, 50, 54-57, and 140-163.

Compounds of Formula VII are also described in the above reference and can be prepared first by reaction of a compound of Formula VIII with, for example, diethyl (ethoxymethylene)malonate (R^2 = H, to afford R^A = Et) or diethyl 2-(1-ethoxyethylidene)malonate (R^2 = Me, to afford R^A = Et), e.g. with heating, followed by reaction with phosphorous oxychloride, again preferably with heating. See for example Intermediate 1 synthesis and G. Yu et. al., *J. Med Chem.*, 2001, 44, 1025-1027 hereinafter, where R^2 = H and R^1 = ethyl; and see Intermediate 58 synthesis hereinafter where R^2 = Me and R^1 = ethyl:



Formula VIII Formula VII, R^A = Et

Where, for example, the desired amino pyrazole of Formula VIII is not commercially available, preparation of the Formula VIII pyrazole can be achieved, for example using methods described by Dorgan et. al. in *J. Chem. Soc., Perkin Trans.* 1980, 1 (4), 938-42, involving reaction of cyanoethyl hydrazine with a suitable aldehyde $R^{1a}CHO$ in a solvent such as ethanol, with heating, followed by reduction, for example reduction with sodium in a solvent such as t-butanol. R^{1a} should be chosen so as to contain one less carbon atom than R^1, for example R^{1a} = methyl will afford R^1 = ethyl.



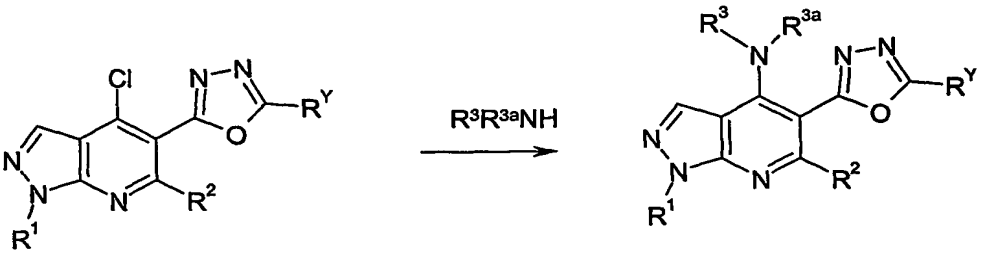
Formula VIII

Alternatively, e.g. where the desired amino pyrazole of Formula VIII is not commercially available, preparation of the compound of Formula VI can be achieved from the compound of Formula VII (e.g. Intermediate 1 wherein R^1 = ethyl), using a generalised version of the reaction scheme shown in Example 43, especially that part relating to conversion of Intermediate 1 to Intermediate 38. In this method: the 4-chloro pyrazolopyridine of Formula VII (e.g. Intermediate 1) is optionally converted to the 4-alkoxy (e.g. C_{1-4}alkoxy such as ethoxy) pyrazolopyridine (e.g. Intermediate 35); the R^1 group is removed (to e.g. Intermediate 36 wherein R^1 is H rather than alkyl), the 4-amino $R^3R^{3a}N$ group is inserted by displacing the 4-chloro or 4-alkoxy group by reaction with $R^3R^{3a}NH$ (e.g. to Intermediate 37); and the pyrazolopyridine is alkylated at N-1 by reacting it with R^1-X^{40} where X^{40} is a group displaceable by the N-1 nitrogen of the pyrazolopyridine in order to re-insert the desired R^1 group (e.g. Intermediate 38

synthesis). X^{40} can for example be a halogen, e.g. Cl, Br or I; or X^{40} can be $-O-SO_2-R^{40}$ where R^{40} is C_{1-4}alkyl, C_{1-2}fluoroalkyl, or phenyl optionally substituted by C_{1-2}alkyl.

Process B

Compounds of formula (I) which are compounds of Formula I(ia) (that is, compounds of formula (I) wherein Het is of sub-formula (ia)) can alternatively be prepared by reaction of a compound of Formula IX with an amine of formula $R^3R^{3a}NH$, preferably in a solvent (e.g. organic solvent) such as ethanol or acetonitrile, and/or preferably in the presence of a base such as DIPEA. Heating may be required to effect the conversion:



Formula IX Formula I(ia)

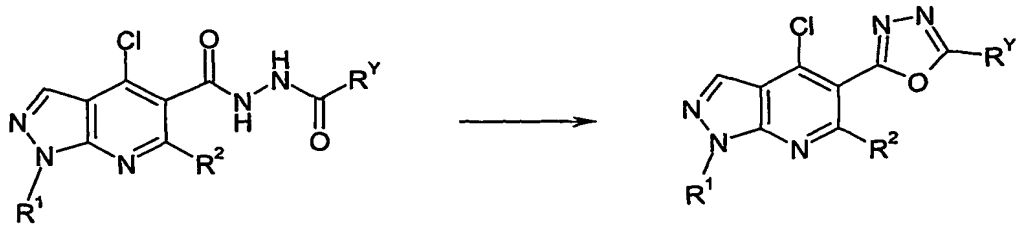
For the reaction of a compound of Formula IX with an amine of formula $R^3R^{3a}NH$ to prepare the compound of Formula I(ia), the reaction conditions, e.g. solvents, mole ratios, temperatures and/or reaction times, can optionally be as described in Examples 9, 10-11 and/or 12-27.

The reaction of Formula IX with $R^3R^{3a}NH$ to give Formula I(ia) can be generalised for any compound of Formula (I), containing any Het group as defined herein, starting from a compound of Formula IXa:

Formula IXa Formula (I)

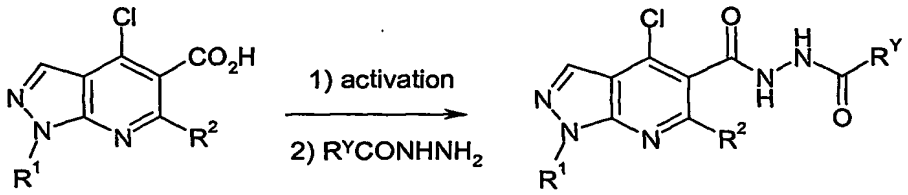
Compounds of Formula IX can themselves be prepared by cyclisation of a compound of Formula X, preferably in the presence of a dehydrating agent such asphosphorous oxychloride or Burgess reagent [(Methoxycarbonylsulphamoyl)triethylammonium hydroxide], in a suitable solvent (e.g. organic solvent, preferably anhydrous) such as

acetonitrile (e.g. for $POCl_3$) or THF and/or DMF (e.g. for Burgess reagent). The reaction may require heating, for example heating to from about 70 to about 150 °C or heating to from about 70 to about 120 °C or heating to from about 70 to about 90 °C:



Formula X Formula IX

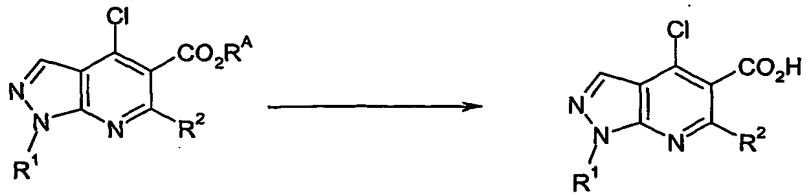
Compounds of Formula X can be prepared by initial activation of an acid of Formula XI, for example with an amide coupling reagent such as EDC/HOBT or with thionyl chloride, followed by reaction of the thus formed activated intermediate with an acid hydrazide of Formula $R^YCONHNH_2$:



Formula XI Formula X

Examples of reactions of the compound of Formula XI to Formula X and of the compound of Formula X to Formula IX are presented in Intermediates 12 to 15.

Acids of Formula XI can themselves be prepared by hydrolysis of an ester of Formula VII (e.g. as described in Process A) using a base such as potassium hydroxide in a solvent such as aqueous dioxane dioxane/water):

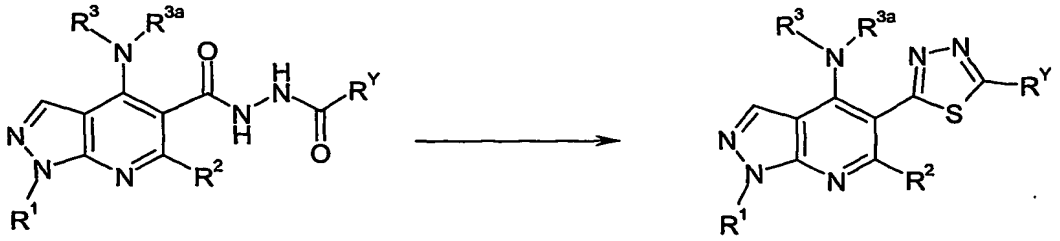


Formula VII Formula XI

Process C

Compounds of Formula XII (that is, compounds of formula (I) wherein Het is of sub-formula (ib)) can be prepared by reaction of a compound of Formula II with a reagent

capable of inserting sulfur, such as Lawesson's reagent, usually in a suitable solvent such as acetonitrile. The reaction may require heating:

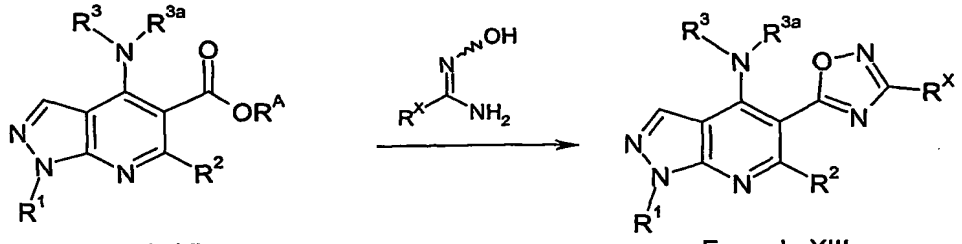


Formula II Formula XII

The reaction conditions, e.g. solvents, mole ratios, temperatures and/or reaction times, can optionally be as described in Examples 4, 5 or 6.

Process D

Compounds of Formula XIII [which are compounds of formula (I) wherein Het is of sub-formula (ic)] can be prepared by reaction of a compound of Formula VI (R^A can be C_{1-6}alkyl such as Et) with an amidoxime of formula $R^XC(=NOH)NH_2$, preferably in the presence of a base such as sodium ethoxide and/or preferably in a suitable solvent (e.g. anhydrous and/or organic solvent) such as ethanol, and preferably in the presence of molecular sieves (e.g. 4 Angstrom and/or powdered molecular sieves) or under other conditions effective for removing water. The reaction mixture may optionally be heated, for example to reflux:



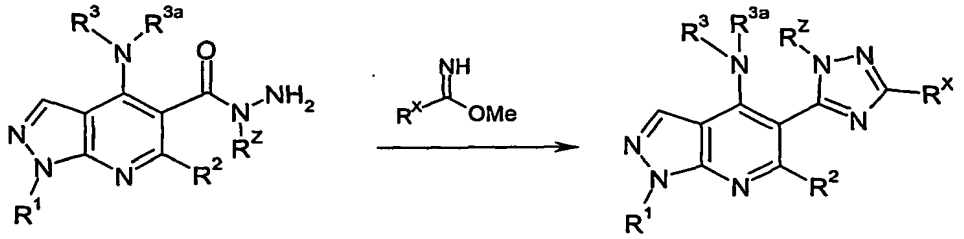
Formula VI Formula XIII

The reaction conditions, e.g. solvents, mole ratios, temperatures and/or reaction times, can optionally be as described in Examples 7, 28-29, 30, 31, 48, 82-84, 92, 93 and/or 178-187.

Process E

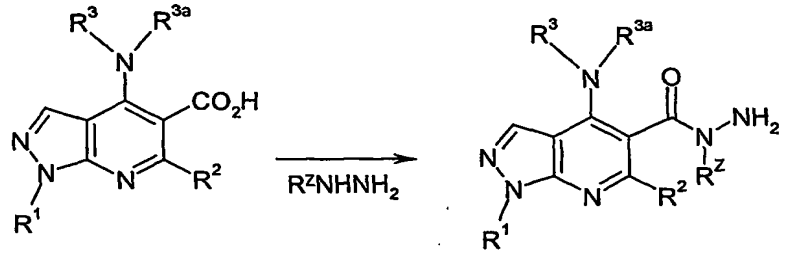
Compounds of Formula XIV (which are compounds of formula (I) wherein Het is of sub-formula (if)) can be prepared by reaction of a compound of Formula XV with a suitable acetimidate R^X-C(=NH)OR^E, where R^E is C_{1-6}alkyl e.g. methyl, (such as

methyl acetimidate (R^X = Me)), preferably in the presence of a base (such as triethylamine or sodium ethoxide) and/or in a suitable solvent (e.g. anhydrous and/or organic solvent) such as ethanol:



Formula XV Formula XIV

Compounds of Formula XV may themselves be prepared by reaction of a compound of Formula III with a suitably substituted hydrazine derivative of Formula R^ZNHNH_2, under coupling conditions. For example a coupling agent such as EDC may be used, e.g. in the presence of hydroxybenzotriazole (HOBT), in a suitable solvent such as DMF:



Formula III Formula XV

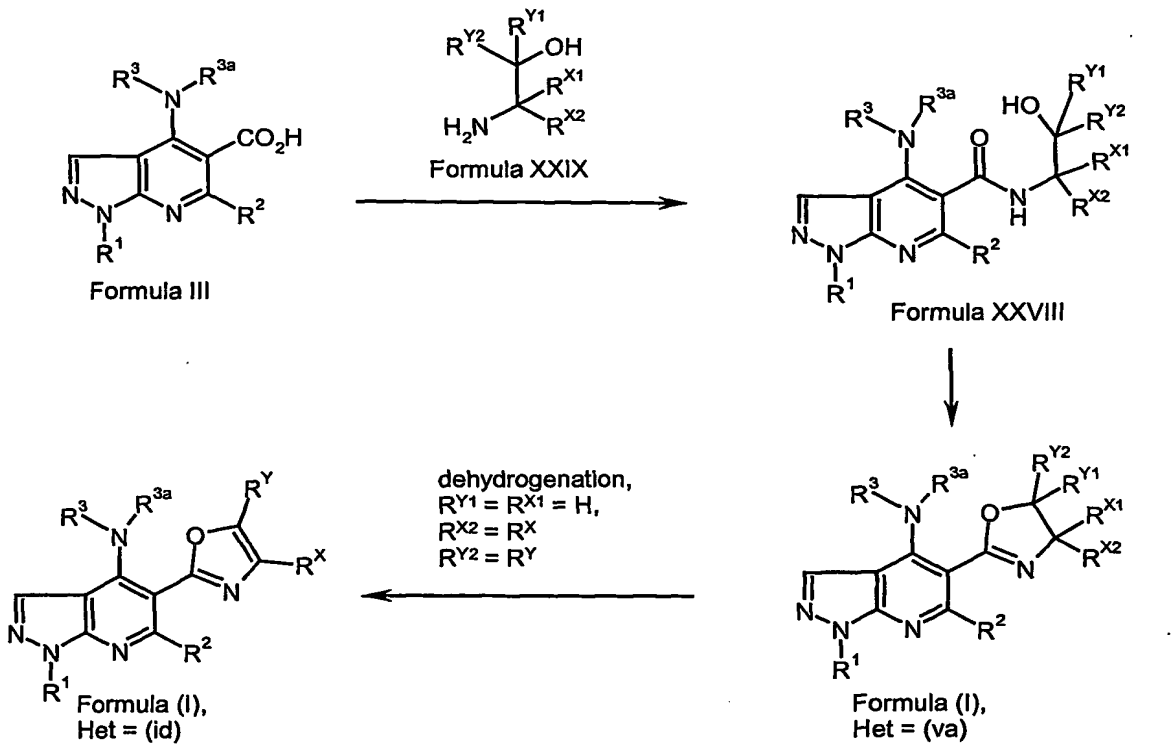
Process F

To make a compound of formula (I) wherein Het is of sub-formula (id) (optionally substituted 1,3-oxazol-2-yl), methods known to the skilled person can be used.

For example, the 5-carboxylic acid compound of Formula III can be converted directly or indirectly to a compound of formula (I) wherein Het is of sub-formula (id) (i.e. to a 5-(optionally-substituted 1,3-oxazol-2-yl)-pyrazolopyridine). Alternatively or additionally, a compound of formula (I), wherein Het is of sub-formula (va) in which R^{X1} and R^{Y1} are H and R^{X1} is R^X and R^{Y1} is R^Y [i.e. the corresponding 5-(optionally-substituted 4,5-dihydro-1,3-oxazol-2-yl)-pyrazolopyridine], can be dehydrogenated to a compound of formula (I) wherein Het is of sub-formula (id); e.g. by the method shown in Example 41 (DBU, CCl_4, CH_3CN, Pyridine) or a modification of this method or by an analogous method for example using an oxidising agent.
The dehydrogenation (oxidation) of the 4,5-dihydro-1,3-oxazol-2-yl compound of formula (I) (wherein Het is of sub-formula (va) in which R^{X1} and R^{Y1} are H and R^{X1} is R^X and R^{Y1} is R^Y) to the corresponding 1,3-oxazol-2-yl compound of formula (I)

wherein Het is of sub-formula (id) can be carried out using reagents and conditions known to the skilled man (see for example the following reviews: T.G. Gant et al., *Tetrahedron*, 1994, 50(8), 2297-2360; M.Reuman et al., *Tetrahedron*, 1985, 41(5), 837-860; and references cited therein). For this dehydrogenation reaction, preferably an oxidising agent is used such as nickel peroxide, manganese dioxide (MnO_2), or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

A compound of formula (I) wherein Het is of sub-formula (va) can be prepared by cyclisation of a compound of Formula XXVIII, for example in the presence of Burgess reagent and/or preferably in a suitable solvent (e.g. organic solvent, preferably anhydrous) such as THF.

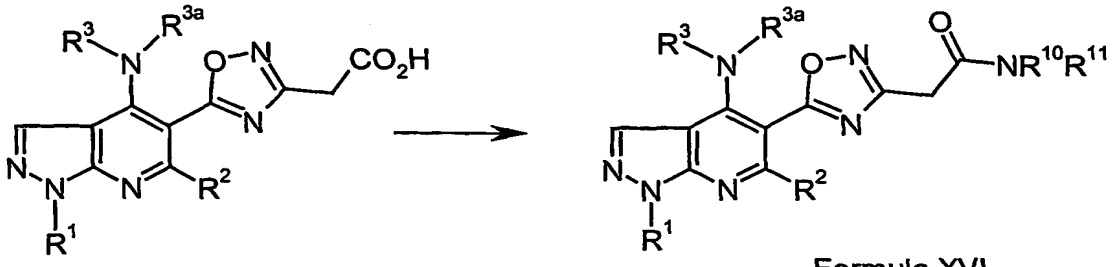


The compound of Formula XXVIII can be prepared from the compound of Formula III by reaction with the compound of Formula XXIX under coupling conditions (e.g. EDC with or without HOBT), optionally in the presence of a base such as Et_3N, and preferably in a suitable solvent such as DMF.

Process G

Compounds of the invention of Formula XVI (1,2,4-oxadiazoles), which are compounds of formula (I) wherein Het is of sub-formula (ic) and R^X is $-CH_2C(O)NR^{10}R^{11}$, can be prepared by reaction of a compound of the Formula XVII with an amine of Formula

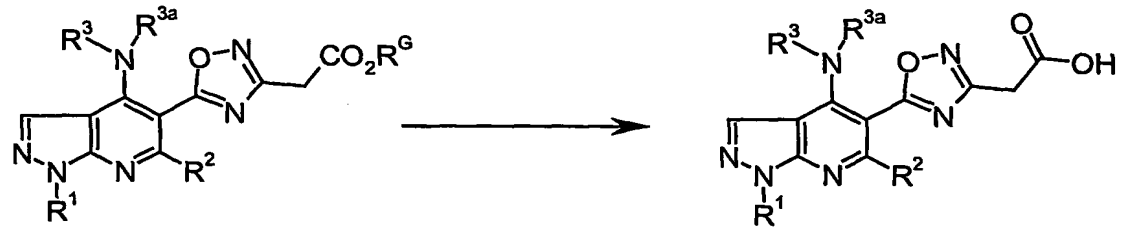
$R^{10}R^{11}NH$, under coupling conditions. Standard coupling conditions can be used known to the skilled person. For example a coupling agent such as TBTU may be used, preferably in the presence of hydroxybenzotriazole. However, it is more preferable that the coupling agent is oxalyl chloride, which in the reaction forms the corresponding acid chloride from the carboxylic acid of the compound of Formula XVII; in this embodiment it is preferable that the acid chloride is not isolated, i.e. the solvent in which it is formed is preferably not removed to a substantial extent. Preferably, whatever the coupling agent / coupling conditions, the reaction is carried out in the presence of a base such as diisopropylethylamine, and/or in a suitable solvent (e.g. organic solvent, preferably anhydrous) such as DMF and/or dicloromethane.



Formula XVII Formula XVI

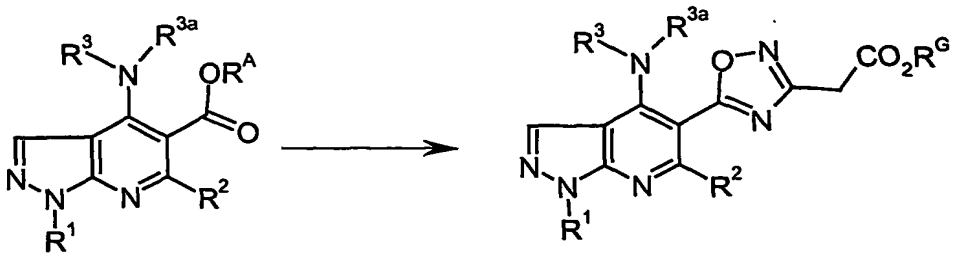
The reaction conditions for the Formula XVII to Formula XVI reaction, e.g. solvents, mole ratios, temperatures and/or reaction times, can optionally be as described in Examples 85-90, 95-96 and/or 148-155.

Compounds of Formula XVII may themselves be prepared by reaction of a compound of Formula XVIII (R^G is preferably ^tBu) with a hydrolysing agent (e.g. an acid such as trifluoroacetic acid) in a solvent such as dichloromethane:



Formula XVIII Formula XVII

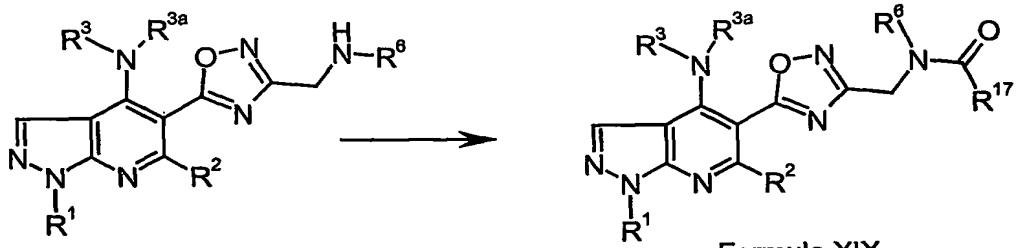
Compounds of Formula XVIII can be prepared by reaction of a compound of Formula VI (R^A = H) with an amidoxime of formula $R^GOC(=O)CH_2C(=NOH)NH_2$ and a coupling agent, for example TBTU, preferably in the presence of hydroxybenzotriazole, preferably in the presence of a base such as diisopropylethylamine and/or in a suitable solvent such as DMF, followed by reaction with 1,1'-carbonyldiimidazole:



Formula VI Formula XVIII

Process H

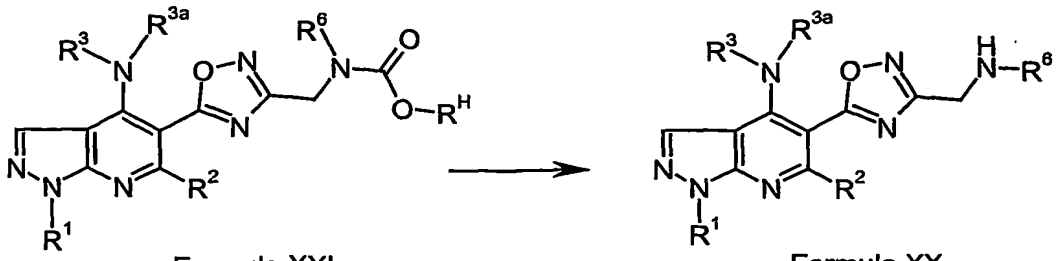
Compounds of Formula XIX, which are compounds of formula (I) wherein Het is of sub-formula (ic) and R^X is $-CH_2-NR^6R^7$ wherein R^7 is $C(O)R^{17}$, may be prepared from compounds of Formula XX. For example, this can be by reaction of the compound of Formula XX with a carboxylic acid $R^{17}COOH$ in the presence of a coupling agent, for example TBTU, preferably with hydroxybenzotriazole, and preferably in the presence of a base such as diisopropylethylamine in a suitable solvent such as DMF. Alternatively or additionally, the compound of Formula XX can be reacted with an activated derivative of the carboxylic acid moiety of $R^{17}COOH$ (e.g. by reaction with an acid chloride $R^{17}C(O)Cl$), preferably in the presence of a base such as diisopropylethylamine and/or in a suitable solvent (e.g. organic) such as dichloromethane and/or chloroform.



Formula XX Formula XIX

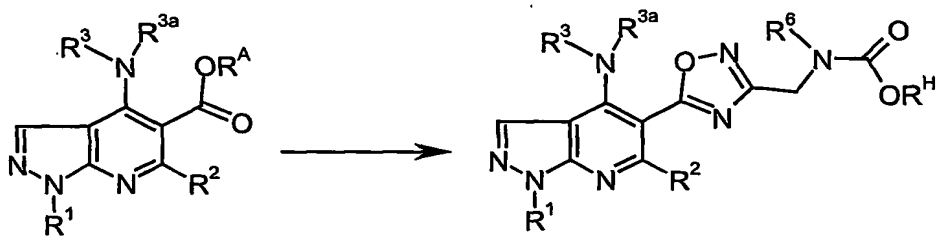
The reaction conditions for the Formula XX to Formula XIX reaction, e.g. solvents, mole ratios, temperatures and/or reaction times, can optionally be as described in any of Examples 159-165.

Compounds of Formula XX, which are compounds of formula (I) wherein Het is of sub-formula (ic) and R^X is $-CH_2-NR^6R^7$ wherein R^7 is H, may be prepared by deprotecting compounds of Formula XXI wherein R^H is benzyl or C_{1-6}alkyl such as ^tBu, e.g. by reaction with an acid such as trifluoroacetic acid (e.g. where R^H is C_{1-6}alkyl such as ^tBu) or by hydrogenation (e.g. where R^H is benzyl), preferably in a suitable solvent such as dichloromethane:



Formula XXI Formula XX

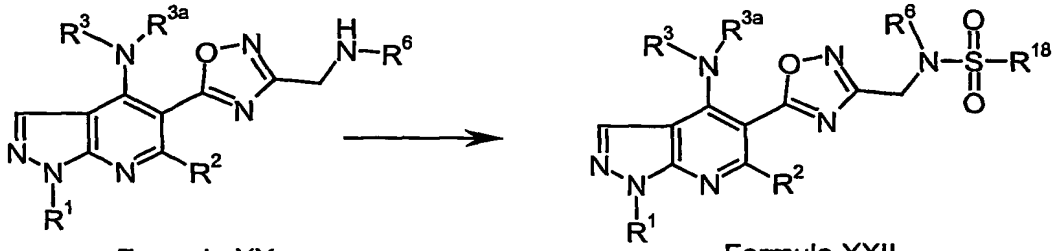
Compounds of Formula XXI can be prepared by reaction of a compound of Formula VI (but wherein R^A is OH) with an amidoxime of formula $R^HOC(=O)N(R^6)CH_2C(=NOH)NH_2$ and a coupling agent, for example TBTU, preferably in the presence of hydroxybenzotriazole, and preferably in the presence of a base such as diisopropylethylamine, and/or preferably in a suitable solvent such as DMF, followed by reaction with a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene:



Formula VI Formula XXI

Process I

Compounds of Formula XXII, which are compounds of formula (I) wherein Het is of sub-formula (ic) and R^X is $-CH_2-NR^6R^7$ wherein R^7 is $-S(O)_2R^{18}$, may be prepared from compounds of Formula XX by reaction with a sulphonyl chloride $R^{18}S(O)_2Cl$, preferably in the presence of a base such as triethylamine and/or pyridine, and/or preferably in a suitable solvent (e.g. organic) such as dichloromethane and/or chloroform:



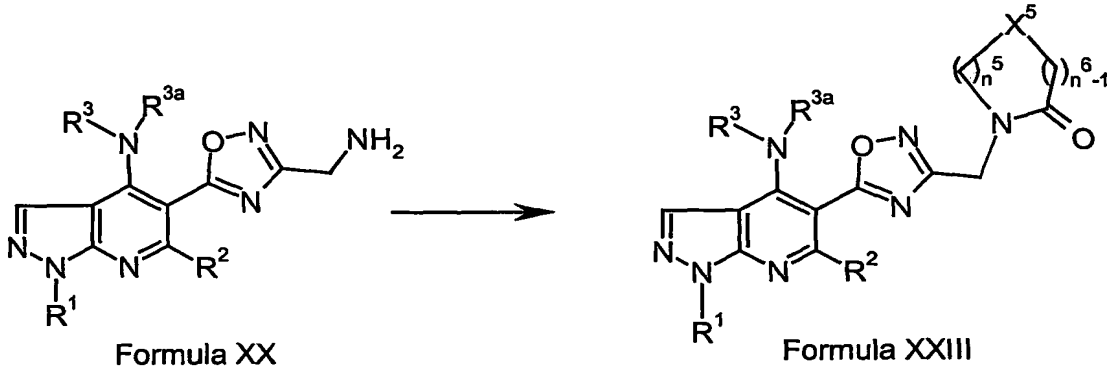
Formula XX Formula XXII

The reaction conditions, e.g. solvents, mole ratios, temperatures and/or reaction times, can optionally be as described in any of Examples 166-172.

Process J

Compounds of Formula XXIII are compounds of formula (I) wherein Het is of sub-formula (ic) and R^X is $-CH_2-NR^6R^7$, wherein R^6 and R^7 together are $-(CH_2)_n{}^5-X^5-(CH_2)_n{}^6-$ in which n^5 and n^6 independently are 2 or 3, and wherein the ring formed by NR^6R^7 is substituted by one oxo (=O) substituent at a carbon atom within $(CH_2)_n{}^6$ which carbon atom is bonded to the nitrogen.

Compounds of Formula XXIII can be prepared by reaction of a compound of the type Formula XX wherein R^6 = H with acid chlorides of the type $X^J-(CH_2)_n{}^5-X^5-(CH_2)(n^6-1)-COCl$, where X^J is a leaving group, preferably in the presence of a base such as triethylamine and/or preferably in a suitable solvent, for example dichloromethane or tetrahydrofuran, preferably followed by treatment with a base such as sodium hydride in a suitable solvent such as DMF. The leaving group X^J can for example be a halogen atom such as Cl, Br or I; or X^J can for example be $-O-SO_2-R^J$ where R^J is C_{1-4}alkyl, C_{1-2}fluoroalkyl, or phenyl optionally substituted by C_{1-2}alkyl e.g. 4-methylphenyl.

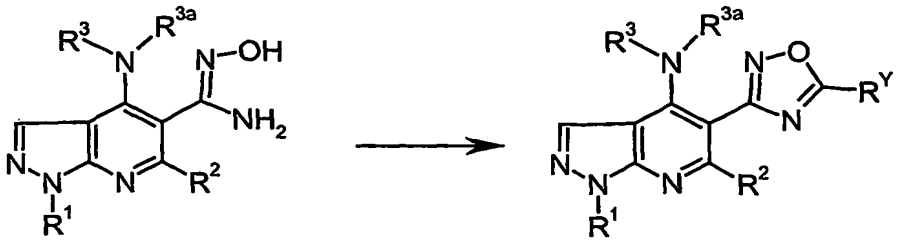


Formula XX Formula XXIII

For examples of reaction conditions for the Formula XX to Formula XXIII reaction, see for example Intermediates 119 and/or 120 and/or subsequent Examples 173 and/or 174.

Process K

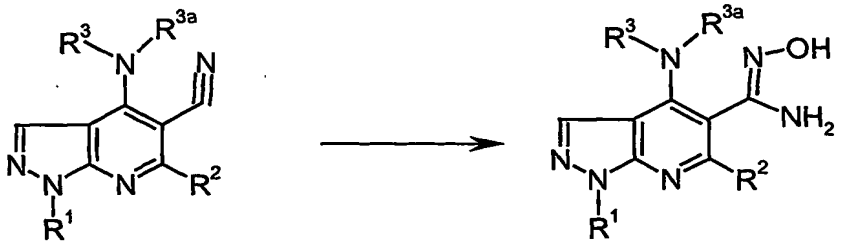
Compounds of the type Formula XXIV, which are compounds of formula (I) wherein Het is of sub-formula (iia), can be prepared from compounds of the type Formula XXV by reaction with $R^YC(O)X^K$ where X^K is a leaving group, preferably in a solvent such as acetic acid, pyridine, diglyme and/or dichloromethane. X^K can for example be chloro; or $R^YC(O)X^K$ can be an anhydride such as $[R^Y(C=O)]_2O$; or $R^YC(O)X^K$ can be an activated carboxylic acid derivative prepared from the reaction of $R^YC(O)OH$ with a coupling reagent such as EDC or TBTU with or without the presence of HOBT.



Formula XXV Formula XXIV

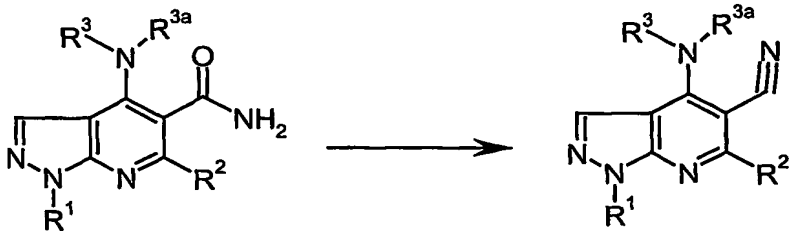
For the Formula XXV to Formula XXIV reaction, the reaction conditions can for example be as described in Examples 188, 189 and/or 190.

Compounds of the type Formula XXV can be prepared from compounds of the type Formula XXVI by reaction with hydroxylamine or a hydroxylamine salt, preferably in the presence of a base such as potassium carbonate, sodium alkoxide or a tertiary amine, and/or preferably in a suitable solvent such as ethanol or methanol:



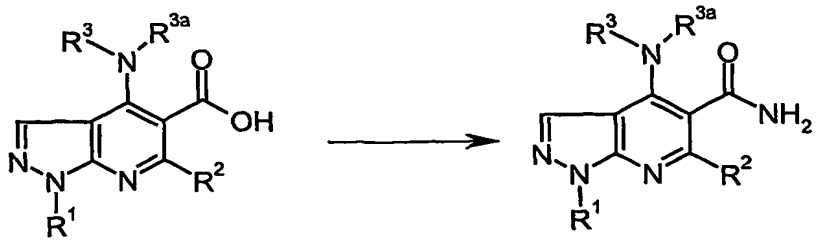
Formula XXVI Formula XXV

Compounds of the type Formula XXVI may themselves be prepared from compounds of Formula XXVII by reaction with a dehydrating agent such as Burgess Reagent, preferably in a solvent, for example tetrahydrofuran:



Formula XXVII Formula XXVI

Compounds of the type Formula XXVII can be prepared from carboxylic acid compounds of Formula III, for example by reaction with thionyl chloride followed by ammonia in a suitable solvent such as dioxane:



Formula III Formula XXVII

Process L - Conversion of a compound of formula (I) or a salt thereof into a different compound of formula (I) or a salt thereof

One compound of formula (I) or salt thereof can be converted into another compound of formula (I) or salt thereof. This conversion preferably comprises or is one or more of the following processes L1 to L10:

L1. An oxidation process. For example, the oxidation process can comprise or be oxidation of an alcohol to a ketone (e.g. using Jones reagent) or oxidation of an alcohol or a ketone to a carboxylic acid.

L2. A reduction process, for example reduction of a ketone or a carboxylic acid to an alcohol.

L3. Acylation, for example acylation of an amine or of a hydroxy group.

L4. Alkylation, for example alkylation of an amine or of a hydroxy group.

L5. Hydrolysis, e.g. hydrolysis of an ester to the corresponding carboxylic acid or salt thereof, for example in the presence of base (e.g. alkali-metal hydroxide, preferably also in the presence of water) or in the presence of acid (e.g. aqueous HCl, or HCl in an anhydrous organic solvent such as dioxane).

The hydrolysis can for example be hydrolysis of an ester compound, in which R^X, R^{X2}, R^Y or R^{Y2} is $-(CH_2)_n{}^{12}-C(O)-OR^{13}$ wherein R^{13} is not a hydrogen atom (H), to the corresponding carboxylic acid wherein R^{13} is a hydrogen atom (H). See for example Example 57 and Intermediate 83.

The hydrolysis can for example be hydrolysis of an ester compound, wherein R^3 is substituted by $-C(O)OR^{23}$ in which R^{23} is C_{1-2}alkyl (e.g. NHR^3 or NR^3R^{3a} is of sub-formula (p8)), to the corresponding carboxylic acid or salt thereof wherein R^{23} is H (e.g. NHR^3 or NR^3R^{3a} is of sub-formula (p7)).

L6. Deprotection, e.g. deprotection (e.g. deacylation or t-butyloxycarbonyl (BOC) removal or benzyloxycarbonyl removal) of an amine group.

L7. Formation of an ester or amide, for example from the corresponding carboxylic acid and/or an activated derivative of the carboxylic acid (e.g. acid chloride or acid anhydride or carboxylic acid activated by a coupling agent).

The amide formation can be formation of an amide compound, in which one or more of R^X, R^{X2}, R^Y and R^{Y2} is $-(CH_2)_n{}^{11}$-C(O)-$NR^{10}R^{11}$, -CH(C_{1-2}alkyl)-C(O)-$NR^{10}R^{11}$, $-CMe_2$-C(O)-$NR^{10}R^{11}$ or cycloalkyl substituted by -C(O)-$NR^{10}R^{11}$, from the corresponding carboxylic acid and/or an activated derivative of the carboxylic acid. For examples of this amide formation, see Examples 58-59 and/or 126-147 for Het = sub-formula (id), and/or Process G herein for Het = sub-formula (ic) (e.g. Examples 85-90, 95-96 and/or 148-155).

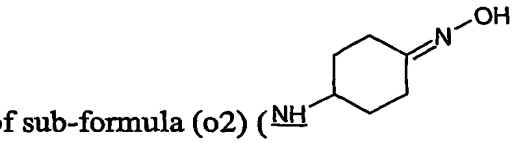
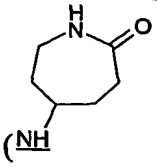
The amide formation can alternatively be formation of an amide compound, in which one or more of R^X, R^{X2}, R^Y and R^{Y2} is $-(CH_2)_n{}^4$-NR^6R^7, -CH(C_{1-2}alkyl)-NR^6R^7, $-CMe_2$-NR^6R^7 or cycloalkyl substituted by -NR^6R^7, wherein R^6 is C(O)R^{17}, from the corresponding carboxylic acid and/or an activated derivative of the carboxylic acid. For one example where Het is of sub-formula (ic) see Process H and/or Examples 159-165.

L8. Conversion of a ketone into the corresponding oxime or oxime ether. This can for example include conversion of an oxo (=O) substituent within R^3, e.g. within the NHR^3 or NR^3R^{3a} sub-formula (o), into an hydroxyimino (=N-OH) or (C_{1-4}alkoxy)imino (=N-OR^{26}) substituent within R^3, e.g. within the NHR^3 or NR^3R^{3a} sub-formula (o2), (o3), (o4) or (o5). This conversion can be carried out in the case of an oxime (hydroxyimino, =N-OH) by reacting hydroxylamine or a salt thereof (e.g. hydroxylamine hydrochloride) with the ketone, or in the case of an oxime ether (C_{1-4}alkoxy)imino, =N-OR^{26}) by reacting C_{1-4}alkoxylamine or a salt thereof (e.g. hydrochloride salt) with the ketone. The reaction is preferably carried out in the presence of a base such as anhydrous potassium carbonate or diisopropylethylamine and/or in a suitable solvent such as acetonitrile. The mixture can be heated e.g. to reflux.

L9. Sulfonylation, e.g. sulfonamide formation by reaction of an amine with a sulfonyl halide e.g. a sulfonyl chloride (e.g. see also Process I).

and/or

L10. Beckmann rearrangement of one compound of formula (I) into another compound of formula (I). Preferably, this uses cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) together with a formamide such as DMF, e.g. at room temperature (see L.D. Luca, *J. Org. Chem.*, 2002, 67, 6272-6274). The Beckmann rearrangement can for example comprise conversion of an (hydroxyimino)cycloalkyl compound of formula (I), e.g. wherein NHR^3

or NR^3R^{3a} is of sub-formula (o2) (), into a single-atom-ring-expanded lactam compound of formula (I), e.g. wherein NHR^3 or NR^3R^{3a} is of sub-formula (m3) ().

The present invention therefore also provides a method of preparing a compound of formula (I) or a salt thereof, comprising :

(a) cyclisation of a compound of formula II to a compound of formula (I) wherein Het is of sub-formula (ia) (that is: to a compound of Formula I(ia), i.e. to an optionally substituted 1,3,4-oxadiazol-2-yl derivative at the 5-position of the pyrazolopyridine ring system), for example in the presence of a dehydrating agent such as phosphorus oxychloride or Burgess reagent, or

(b) reaction of a compound of formula IXa with an amine of formula $R^3R^{3a}NH$ to form a compound of formula (I), preferably in a solvent (e.g. organic solvent) and/or preferably in the presence of a base, or

(c) cyclisation of a compound of formula II to a compound of formula (I) wherein Het is of sub-formula (ib) (i.e. to a compound of Formula XII i.e. to an optionally substituted 1,3,4-thiadiazol-2-yl derivative at the 5-position of the pyrazolopyridine ring system), for example in the presence of an agent capable of introducing sulfur such as Lawesson's reagent, or

(d) reaction of a compound of formula VI, wherein R^A is C_{1-6}alkyl such as Et, with an amidoxime of formula $R^XC(=NOH)NH_2$ or a salt thereof, preferably in the presence of a base such as sodium ethoxide and/or preferably in a suitable solvent (e.g. anhydrous and/or organic solvent) such as ethanol; or

(e) reaction of a compound of formula XV with an acetimidate R^X-$C(=NH)OR^E$, where R^E is C_{1-6}alkyl, to prepare a compound of formula (I) wherein Het is of sub-formula (if) (i.e. to a compound of Formula XIV, i.e. to an optionally substituted 1,2,4-triazol- 3-yl or 5-yl derivative at the 5-position of the pyrazolopyridine ring system), preferably in the presence of a base (such as triethylamine or sodium ethoxide) and/or in a suitable solvent (e.g. anhydrous and/or organic solvent) such as ethanol; or

(f)(i) converting directly or indirectly a compound of Formula III to a compound of formula (I) wherein Het is of sub-formula (id); and/or (f)(ii) dehydrogenating a compound of formula (I), wherein Het is of sub-formula (va) in which R^{X1} and R^{Y1} are H and R^{X1} is R^X and R^{Y1} is R^Y, to a compound of formula (I) wherein Het is of sub-formula (id); or

(f)(iii) cyclisation of a compound of Formula XXVIII, for example in the presence of Burgess reagent and/or preferably in a suitable solvent, to prepare a compound of formula (I) wherein Het is of sub-formula (va); or

(g) reaction of a compound of the Formula XVII with an amine of Formula $R^{10}R^{11}NH$ under coupling conditions, to prepare a compound of formula (I) wherein Het is of sub-formula (ic) and R^X is $-CH_2C(O)NR^{10}R^{11}$ (i.e. to prepare a compound of Formula XVI), the reaction preferably being carried out in the presence of a base such as diisopropylethylamine, and/or preferably in a suitable solvent (e.g. organic solvent, preferably anhydrous) such as DMF and/or dicloromethane, and/or preferably in the presence of oxalyl chloride; or

(h) conversion of a compound of Formula XX into a compound of formula (I) wherein Het is of sub-formula (ic) and R^X is $-CH_2-NR^6R^7$ wherein R^7 is $C(O)R^{17}$ (i.e. into a compound of Formula XIX), preferably either by reaction of the compound of Formula XX with a carboxylic acid $R^{17}COOH$ in the presence of a coupling agent, and/or by reaction of the compound of Formula XX with an activated derivative of the carboxylic acid moiety of $R^{17}COOH$ (e.g. $R^{17}C(O)Cl$), preferably in the presence of a base and/or a suitable solvent; or

(i) reaction of a compound of Formula XX with a sulphonyl chloride $R^{18}S(O)_2Cl$ to prepare a compound of formula (I) wherein Het is of sub-formula (ic) and R^X is $-CH_2-NR^6R^7$ wherein R^7 is $-S(O)_2R^{18}$ (i.e. to prepare a compound of Formula XXII), preferably in the presence of a base such as triethylamine and/or pyridine, and/or preferably in a suitable solvent such as dichloromethane and/or chloroform; or

(j) reaction of a compound of Formula XX wherein R^6 = H with an acid chloride of formula $X^J-(CH_2)_n{}^5-X^5-(CH_2)_{(n^6-1)}-COCl$, where X^J is a leaving group (X^J preferably being a halogen atom or $-O-SO_2-R^J$ where R^J is C_{1-4}alkyl, C_{1-2}fluoroalkyl, or phenyl optionally substituted by C_{1-2}alkyl), to prepare a compound of formula (I) wherein Het is of sub-formula (ic) and R^X is $-CH_2-NR^6R^7$, wherein R^6 and R^7 together are $-(CH_2)_n{}^5-X^5-(CH_2)_n{}^6-$ in which n^5 and n^6 independently are 2 or 3, and wherein the ring formed by NR^6R^7 is substituted by one oxo (=O) substituent at a carbon atom within $(CH_2)_n{}^6$ which carbon atom is bonded to the nitrogen (i.e. to prepare a compound of

Formula XXIII); the reaction preferably being in the presence of a base and/or in a suitable solvent, and/or preferably being followed by treatment with a base; or

(k) reaction of a compound of Formula XXV with $R^YC(O)X^K$ where X^K is a leaving group, to prepare a compound of formula (I) wherein Het is of sub-formula (iia) (i.e. to prepare a compound of Formula XXIV); or

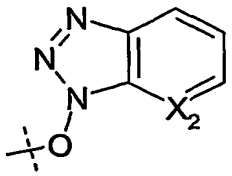
(L) conversion of a compound of formula (I) or a salt thereof into a different compound of formula (I) or a salt thereof;

and optionally converting the compound of formula (I) into a salt e.g. a pharmaceutically acceptable salt.

Salt formation processes may optionally be as described elsewhere herein.

Preferred features of methods (a), (b), (c), (d), (e), (f)(i), (f)(ii), (f)(iii), (g), (h), (i), (j), (k), and (L), independently of each other, are preferably as described above for Processes A, B, C, D, E, F, G, H, I, J, K, and L with all necessary changes being made. For example, the conversion process (L) preferably comprises or is one or more of processes L1 to L10 described herein, e.g. hereinabove.

In any of the methods which involve reaction of a carboxylic acid and/or an activated carboxylic acid derivative with an amine to form an amide, the activated carboxylic acid derivative preferably comprises a $-C(O)X^{11}$ group in place of the COOH, wherein X^{11} is a leaving group substitutable by an amine. For example X^{11} can be Cl (wherein the activated derivative = the acid chloride) or -OC(O)R (wherein the activated derivative = an anhydride). Alternatively, the activated carboxylic acid derivative can be an activated ester wherein the leaving group X^{11} is



X_2 = CH or N

The latter activated carboxylic acid derivative can be formed from the carboxylic acid (X^{11} = OH) either:
(a) by reaction of the carboxylic acid with a carbodiimide such as EDC, which is 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide and is also 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or a salt thereof e.g. hydrochloride salt,
preferably followed by reaction of the resulting product with 1-hydroxybenzotriazole (HOBT); reaction (a) usually being carried out in the presence of a solvent (preferably

anhydrous) such as dimethyl formamide (DMF) or acetonitrile and/or preferably under anhydrous conditions and/or usually at room temperature (e.g. about 20 to about 25 °C); or

(b) by reaction with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) or O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) , preferably in the presence of a base such as diisopropylethylamine ($^{i}Pr_2NEt$ = DIPEA), and usually in the presence of a solvent such as dimethyl formamide (DMF) or acetonitrile and/or preferably under anhydrous conditions and/or usually at room temperature (e.g. about 20 to about 25 °C).

The present invention also provides: (m) a method of preparing a pharmaceutically acceptable salt of a compound of formula (I) comprising conversion of the compound of formula (I) or a salt thereof into the desired pharmaceutically acceptable salt thereof.

The present invention also provides a compound of formula (I) or a salt thereof, prepared by a method as defined herein.

Medical uses

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance in a mammal such as a human. The compound or salt can be for use in the treatment and/or prophylaxis of any of the diseases / conditions described herein (e.g. for use in the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal) and/or for use as a phosphodiesterase inhibitor e.g. for use as a phosphodiesterase 4 (PDE4) inhibitor. "Therapy" may include treatment and/or prophylaxis.

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament (e.g. pharmaceutical composition) for the treatment and/or prophylaxis of any of the diseases / conditions described herein in a mammal such as a human, e.g. for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human.

Also provided is a method of treatment and/or prophylaxis of any of the diseases / conditions described herein in a mammal (e.g. human) in need thereof, e.g. a method of treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal (e.g. human) in need thereof, which method comprises administering to the mammal (e.g. human) a therapeutically effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable salt thereof.

Phosphodiesterase 4 inhibitors are thought to be useful in the treatment and/or prophylaxis of a variety of diseases / conditions, especially inflammatory and/or allergic diseases, in mammals such as humans, for example: asthma, chronic obstructive pulmonary disease (COPD) (e.g. chronic bronchitis and/or emphysema), atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, multiple sclerosis, cognitive impairment (e.g. in a neurological disorder such as Alzheimer's disease), depression, or pain. Ulcerative colitis and/or Crohn's disease are collectively often referred to as inflammatory bowel disease.

In the treatment and/or prophylaxis, the inflammatory and/or allergic disease is preferably chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis or allergic rhinitis in a mammal (e.g. human). More preferably, the treatment and/or prophylaxis is of COPD or asthma in a mammal (e.g. human).

PDE4 inhibitors are thought to be effective in the treatment of asthma (e.g. see M.A.Giembycz, *Drugs*, Feb. 2000, 59(2), 193-212; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and refs cited therein).

PDE4 inhibitors are thought to be effective in the treatment of COPD (e.g. see S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and refs cited therein). COPD is often characterised by the presence of airflow obstruction due to chronic bronchitis and/or emphysema (SL Wolda, *Emerging Drugs*, 2000, 5(3), 309-319).

PDE4 inhibitors are thought to be effective in the treatment of allergic rhinitis (e.g. see B.M. Schmidt et al., *J. Allergy & Clinical Immunology*, 108(4), 2001, 530-536).

PDE4 inhibitors are thought to be effective in the treatment of rheumatoid arthritis and multiple sclerosis (e.g. see H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; and A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473;

and refs cited therein). See e.g. A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473 and refs cited therein for atopic dermatitis use.

PDE4 inhibitors have been suggested as having analgesic properties and thus being effective in the treatment of pain (A.Kumar et al., *Indian J. Exp. Biol.*, 2000, 38(1), 26-30).

In the invention, the treatment and/or prophylaxis can be of cognitive impairment e.g. cognitive impairment in a neurological disorder such as Alzheimer's disease. For example, the treatment and/or prophylaxis can comprise cognitive enhancement e.g. in a neurological disorder. See for example: H.T.Zhang et al. in: *Psychopharmacology*, June 2000, 150(3), 311-316 and *Neuropsychopharmacology*, 2000, 23(2), 198-204; and T. Egawa et al., *Japanese J. Pharmacol.*, 1997, 75(3), 275-81.

PDE4 inhibitors such as rolipram have been suggested as having antidepressant properties (e.g. J. Zhu et al., *CNS Drug Reviews*, 2001, 7(4), 387-398; O'Donnell, *Expert Opinion on Investigational Drugs*, 2000, 9(3), 621-625; and H.T. Zhang et al., *Neuropsychopharmacology*, October 2002, 27(4), 587-595).

Pharmaceutical compositions and dosing

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers and/or excipients.

The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

The invention also provides a method of preparing a pharmaceutical composition comprising a compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers and/or excipients,

the method comprising mixing the compound or salt with the one or more pharmaceutically acceptable carriers and/or excipients.

The invention also provides a pharmaceutical composition prepared by said method.

The compounds of formula (I) and/or the pharmaceutical composition may be administered, for example, by oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. Accordingly , the pharmaceutical composition is preferably suitable for oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. More preferably, the pharmaceutical

composition is suitable for inhaled or oral administration, e.g. to a mammal such as a human. Inhaled administration involves topical administration to the lung e.g. by aerosol or dry powder composition. Oral administration to a human is most preferred.

A pharmaceutical composition suitable for oral administration can be liquid or solid; for example it can be a syrup, suspension or emulsion, a tablet, a capsule or a lozenge.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutically acceptable liquid carrier(s), for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

In one preferable embodiment, the pharmaceutical composition is in unit dose form such as a tablet or capsule for oral administration, e.g. for oral administration to a human.

A pharmaceutical composition suitable for oral administration being a tablet can comprise one or more pharmaceutically acceptable carriers and/or excipients suitable for preparing tablet formulations. The carrier can for example be or include lactose, cellulose (for example microcrystalline cellulose), or mannitol. The tablet can also or instead contain one or more pharmaceutically acceptable excipients, for example a binding agent such as hydroxypropylmethylcellulose or povidone (polyvinylpyrollidone), a lubricant e.g. an alkaline earth metal stearate such as magnesium stearate, and/or a tablet disintegrant such as sodium starch glycollate, croscarmellose sodium, or crospovidone (cross-linked polyvinylpyrollidone). The pharmaceutical composition being a tablet can be prepared by a method comprising the steps of: (i) mixing the compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, with the one or more pharmaceutically acceptable carriers and/or excipients, (ii) compressing the resulting mixture (which is usually in powder form) into tablets, and (iii) optionally coating the tablet with a tablet film-coating material.

A pharmaceutical composition suitable for oral administration being a capsule can be prepared using encapsulation procedures. For example, pellets or powder containing the active ingredient can be prepared using a suitable pharmaceutically acceptable carrier and then filled into a hard gelatin capsule. Alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutically acceptable carrier, for example an aqueous gum or an oil and the dispersion or suspension then filled into a soft gelatin capsule.

A parenteral composition can comprise a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil. Alternatively, the solution can be lyophilised; the lyophilised parenteral pharmaceutical composition can be reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, drops, gels or dry powders.

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide, or an organic propellant such as a chlorofluorocarbon (CFC) or hydrofluorocarbon (HFC). Suitable CFC propellants include dichlorodifluoromethane, trichlorofluoromethane and dichlorotetrafluoroethane. Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser.

Particle size reduction of compound of formula (I) or salt thereof

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the compound or salt of formula (I) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. Micronisation usually involves subjecting the compound/salt to collisional and abrasional forces in a fast-flowing circular or spiral/vortex-shaped airstream often including a cyclone component. The preferable particle size (e.g. D50 value) of the size-reduced (e.g. micronised) compound or salt is about 0.5 to about 10 microns, e.g. about 1 to about 5 microns (e.g. as measured using laser diffraction). For example, it is preferable for the compound or salt of formula (I) to have a particle size defined by: a D10 of about 0.3 to about 3 microns (e.g. about 1 micron), and/or a D50 of about 1 to about 5 microns (e.g. about 2-5 or about 2-3 microns), and/or a D90 of about 2 to about 20 microns or about 3 to about 10 microns (e.g. about 5-8 or about 5-6 microns); for example as measured using laser diffraction. The laser diffraction measurement can use a dry method (suspension of compound/salt in airflow crosses laser beam) or a wet method [suspension of compound/salt in liquid dispersing medium, such as isooctane or (e.g. if compound soluble in isooctane) 0.1% Tween 80 in water, crosses laser beam]. With laser diffraction, particle size is preferably calculated using the Fraunhofer calculation; and/or preferably a Malvern Mastersizer or Sympatec apparatus is used for measurement.

An illustrative non-limiting example of a small-scale micronisation process is now given:

Micronisation Example

- Purpose: To micronize a compound of formula (I) or a salt thereof – in particular one of the Examples of the invention (described hereinafter) – usually in an amount of approximately 600-1000 mg, using a Jetpharma MC1 micronizer.

- The parent (unmicronised) and micronised materials are analyzed for particle size by laser diffraction and crystallinity by PXRD.

Equipment and material

Equipment/material	Description and specification
Jetpharma MC1 Micronizer	Nitrogen supply: Air tank with 275psi rate tubing
Analytical balance	Sartorius Analytical
Top loader balance	Mettler PM400
Digital Caliper	VWR Electronic caliper
Vibrational spatula	Auto-spat Dispenser
Materials to be micronised	(not yet performed)

The Jetpharma MC1 Micronizer comprises a horizontal disc-shaped milling housing having: a tubular compound inlet (e.g. angled at ca. 30degrees to the horizontal) for entry of a suspension of unmicronised compound of formula (I) or salt in an gasflow, a separate gas inlet for entry of gases, a gas outlet for exit of gases, and a collection vessel for collecting micronised material. The milling housing has two chambers: an outer annular chamber in gaseous connection with the gas inlet the chamber being for receiving pressurised gas (e.g. air or nitrogen), an disc-shaped inner milling chamber within and coaxial with the outer chamber for micronising the input compound / salt, the two chambers being separated by an annular wall. The annular wall (ring R) has a plurality of narrow-bored holes connecting the inner and outer chambers and circumferentially-spaced-apart around the annular wall. The holes open into the inner chamber directed at an angle (directed part-way between radially and tangentially), and in use act as nozzles directing pressurised gas at high velocity from the outer chamber into the inner chamber and in an inwardly-spiral path (vortex) around the inner chamber (cyclone). The compound inlet is is gaseous communication with the inner chamber via a nozzle directed tangentially to the inner chamber, within and near to the annular wall. Upper and lower broad-diameter exit vents in the central axis of the the inner milling chamber connect to (a) (lower exit) the collection vessel which has no air outlet, and (b) (upper exit) the gas outlet which leads to a collection bag, filter and a gas exhaust. Inside the tubular compound inlet and longitudinally-movable within it is positioned a venturi inlet (V) for entry of gases. The compound inlet also has a bifurcation connecting to an upwardly-directed material inlet port for inputting material.

In use, the narrow head of the venturi inlet (V) is preferably positioned below and slightly forward of the material inlet port so that when the venturi delivers pressurised gas (eg air or nitrogen) the feed material is sucked into the gasstream thorough the compound inlet and accelerates it into the inner milling chamber tangentially at a subsonic speed. Inside the milling chamber the material is further accelerated to a supersonic speed by the hole/nozzle system around the ring (R) (annular wall) of the milling chamber. The nozzles are slightly angled so that the acceleration pattern of the material is in the form of

an inwardly-directed vortex or cyclone. The material inside the milling chamber circulates rapidly and particle collisions occur during the process, causing larger particles to fracture into smaller ones. "Centrifugal" acceleration in the vortex causes the larger particles to remain at the periphery of the inner chamber while progressively smaller particles move closer to the center until they exit the milling chamber, generally through the lower exit, at low pressure and low velocity. The particles that exit the milling chamber are heavier than air and settle downward thorugh the lower exit into the collection vessel, while the exhaust gas rises (together with a miinority of small particles of micronised material) and escapes into the atmosphere at low pressure and low velocity.

Procedure:

The micronizer is assembled. The venturi protrusion distance from input port is adjusted to 1.0cm respectively (e.g. so that the narrow head of the venturi inlet is positioned below and slightly forward of the material inlet port) and is measured with a micro-caliper to make sure that it is inserted correctly. The ring (R) and venturi (V) pressures are adjusted according to the values specified in the experimental design (refer to experimental section below) by adjusting the valves on the pressure gauges on the micronizer. The setup is checked for leakage by observing if there is any fluctuation in the reading of the pressure gauges.

Note that the venturi (V) pressure is kept at least 2 bars greater than the ring (R) pressure to prevent regurgitation of material, e.g. outwardly from the material inlet port.

Balance performance is checked with calibration weights. Specified amount of the parent material (see section on experimental run) is weighed into a plastic weigh boat. The material is then fed into the micronizer using a vibrational spatula (e.g. V-shaped in cross-section) at a specified feed rate. The material feeding time and equipment pressures are monitored during the micronization process.

Upon completion of the micronising run, the nitrogen supply is shut off and the collection bag is tapped to allow particles to settle into the recovery / collection vessel at the bottom of the micronizer. The collection bag is removed and set aside. The micronised powder in the recovery vessel (collection vessel) and the cyclone (above the recovery vessel) are collected separately into different weighed+labelled collection vials. The weight of the micronised material is recorded. The micronizer is disassembled and residual PDE4 compound on the micronizer inner surface is rinsed with 70/30 isopropyl alcohol / water and collected into a flask. The micronizer is then thoroughly cleaned by rinsing and wiping with suitable solvent and dried before subsequent runs are performed.

Preferred Experimental Parameters
Balance(s) Used: Sartorius analytical
Venturi outlet insertion depth: 10.0 mm

Proc-edure no.	Material input amount (g)	Venturi (V) / ring (R) Pressure	Intended feed-rate	Time needed to feed	Actual feed-rate (g/min)

		(bar)		material (min+sec)	
1	0.8795g	V= 10 bar R= 6 bar	200 mg/min	4 min 51 sec	0.181 g/min
2	0.9075g	V= 8 bar R= 5.5 bar	200 mg/min	4 min 43 sec	192 mg/min

The above preferred or optional parameters can be varied using the skilled person's knowledge.

Yield calculations

% yield = [(Material from vessel + Material from cyclone)/Material input amount] x100

In general, very approximately 50-75 % yields are achievable using this method.

Dry powder inhalable compositions

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the pharmaceutical composition is a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose or starch, the compound of formula (I) or salt thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine, mannitol, trehalose and/or magnesium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of formula (I) or salt thereof. The lactose is preferably lactose hydrate e.g. lactose monohydrate and/or is preferably inhalation-grade and/or fine-grade lactose. Preferably, the particle size of the lactose is defined by 90% or more (by weight or by volume) of the lactose particles being less than 1000 microns (micrometres) (e.g. 10-1000 microns e.g. 30-1000 microns) in diameter, and/or 50% or more of the lactose particles being less than 500 microns (e.g. 10-500 microns) in diameter. More preferably, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 300 microns (e.g. 10-300 microns e.g. 50-300 microns) in diameter, and/or 50% or more of the lactose particles being less than 100 microns in diameter. Optionally, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 100-200 microns in diameter, and/or 50% or more of the lactose particles being less than 40-70 microns in diameter. Most importantly, it is preferable that about 3 to about 30% (e.g. about 10%) (by weight or by volume) of the particles are less than 50 microns or less than 20 microns in diameter. For example, without limitation, a suitable inhalation-grade lactose is E9334 lactose (10% fines) (Borculo Domo Ingredients, Hanzeplein 25, 8017 JD Zwolle, Netherlands).

In the dry powder inhalable composition, preferably, the compound of formula (I) or salt thereof is present in about 0.1% to about 70% (e.g. about 1% to about 50%, e.g. about 5% to about 40%, e.g. about 20 to about 30%) by weight of the composition.

An illustrative non-limiting example of a dry powder inhalable composition follows:

Dry Powder Formulation Example - Dry powder Lactose Blend Preparation

Using a size-reduced e.g. micronised form of the compound of formula (I) or salt thereof (e.g. as prepared in the Micronisatrion Example above), the dry powder blend is prepared by mixing the required amount of the compound/salt (e.g. 10 mg, 1% w/w) with inhalation-grade lactose containing 10% fines (e.g. 990 mg, 99% w/w) in a Teflon™ (polytetrafluoroethene) pot in a Mikro-dismembrator ball-mill (but without a ball bearing) at ¾ speed (ca. 2000-2500 rpm) for about 4 hours at each blend concentration. The Mikro-dismembrator (available from B. Braun Biotech International, Schwarzenberger Weg 73-79, D-34212 Melsungen, Germany; www.bbraunbiotech.com) comprises a base with an upwardly-projecting and sidewardly-vibratable arm to which is attached the Teflon ™ pot. The vibration of the arm achieves blending.

Other blends: 10% w/w compound/salt (50 mg) + 90% w/w lactose (450 mg, inhalation-grade lactose containing 10% fines).

Serial dilution of the 1% w/w blend can achieve e.g. 0.1% and 0.3% w/w blends.

Dry powder inhalation devices

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (e.g. containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose, e.g. of the dry powder composition, can be administered by inhalation via a device such as the DISKUS ™ device, marketed by GlaxoSmithKline. The DISKUS ™ inhalation device is usually substantially as described in GB 2,242,134 A, and in such device at least one container for the pharmaceutical composition in powder form (the at least one container preferably being a plurality of sealed dose containers mounted longitudinally in a strip or ribbon) is defined between two members peelably secured to one another; the device comprises: means defining an opening station for the said at least one container; means for peeling the members apart at the opening station to open the container; and an outlet, communicating with the opened container, through which a user can inhale the pharmaceutical composition in powder form from the opened container.

Unit dose form and dosing regimens

Preferably the composition is in unit dose form such as a tablet or capsule for oral administration, e.g. for oral administration to a human.

In the pharmaceutical composition, a or each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg, more preferably 0.5 to 1000 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. A or each dosage unit for nasal or inhaled administration

preferably contains from 0.001 to 50 mg, more preferably 0.01 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

A pharmaceutically acceptable compound or salt of the invention is preferably administered to a mammal (e.g. human) in a daily oral or parenteral dose of 0.001 mg to 50 mg per kg body weight per day (mg/kg/day), for example 0.01 to 20 mg/kg/day or 0.03 to 10 mg/kg/day or 0.1 to 2 mg/kg/day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

A pharmaceutically acceptable compound or salt of the invention is preferably administered to a mammal (e.g. human) in a daily nasal or inhaled dose of: 0.0001 to 5 mg/kg/day or 0.0001 to 1 mg/kg/day, e.g. 0.001 to 1 mg/kg/day or 0.001 to 0.3 mg/kg/day or 0.001 to 0.1 mg/kg/day or 0.005 to 0.3 mg/kg/day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The pharmaceutically acceptable compounds or salts of the invention is preferably administered in a daily dose (for an adult patient) of, for example, an oral or parenteral dose of 0.01 mg to 3000 mg per day or 0.5 to 1000 mg per day e.g. 2 to 500 mg per day, or a nasal or inhaled dose of 0.001 to 300 mg per day or 0.001 to 50 mg per day or 0.01 to 30 mg per day or 0.01 to 5 mg per day or 0.02 to 2 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

Combinations

The compounds, salts and/or pharmaceutical compositions according to the invention may also be used in combination with another therapeutically active agent, for example, a β_2 adrenoreceptor agonist, an anti-histamine, an anti-allergic or an anti-inflammatory agent.

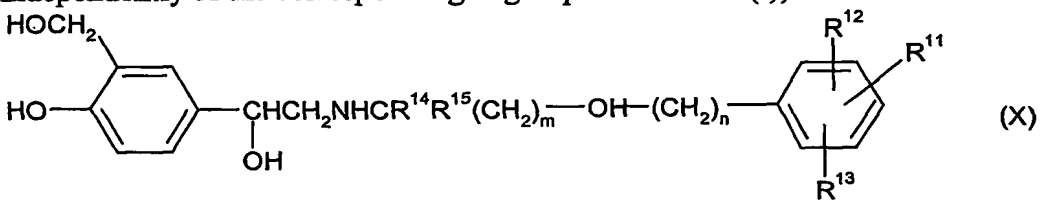
The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with another therapeutically active agent, for example, a β_2-adrenoreceptor agonist, an anti-histamine, an anti-allergic, an anti-inflammatory agent or an antiinfective agent.

Preferably, the β_2-adrenoreceptor agonist is salmeterol (eg as racemate or a single enantiomer such as the R-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline, or a salt thereof (e.g. pharmaceutically acceptable salt thereof), for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. Long-acting β_2-adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 12-24 hour period such as salmeterol or formoterol. Preferably, the β_2-adrenoreceptor agonist is for inhaled administration, e.g. once per day and/or for simultaneous inhaled administration; and more preferably the β_2-adrenoreceptor agonist is in particle-size-reduced form e.g. as defined herein. Preferably, the β_2-adrenoreceptor agonist combination is for treatment and/or

prophylaxis of COPD or asthma. Salmeterol or a pharmaceutically acceptable salt thereof, e.g. salmeterol xinofoate, is preferably administered to humans at an inhaled dose of 25 to 50 micrograms twice per day (measured as the free base). The combination with a β_2-adrenoreceptor agonist can be as described in WO 00/12078.

Preferred long acting β_2-adrenoreceptor agonists include those described in WO 02/066422A, WO 03/024439, WO 02/070490 and WO 02/076933.

Especially preferred long-acting β_2-adrenoreceptor agonists include compounds of formula (X) (described in WO 02/066422) (note that the R groups therein are defined independently of the corresponding R groups of formula (I)):



(X)

or a salt or solvate thereof, wherein in formula (X):
m is an integer of from 2 to 8;
n is an integer of from 3 to 11,
with the proviso that m + n is 5 to 19,
R^{11} is $-XSO_2NR^{16}R^{17}$ wherein X is $-(CH_2)_p-$ or C_{2-6} alkenylene;
R^{16} and R^{17} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $C(O)NR^{18}R^{19}$, phenyl, and phenyl (C_{1-4}alkyl)-,
or R^{16} and R^{17}, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring, and R^{16} and R^{17} are each optionally substituted by one or two groups selected from halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, hydroxy-substituted C_{1-6}alkoxy, $-CO_2R^{18}$, $-SO_2NR^{18}R^{19}$, $-CONR^{18}R^{19}$, $-NR^{18}C(O)R^{19}$, or a 5-, 6- or 7-membered heterocylic ring;
R^{18} and R^{19} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, and phenyl (C_{1-4}alkyl)-; and
p is an integer of from 0 to 6, preferably from 0 to 4;
R^{12} and R^{13} are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, phenyl, and C_{1-6}haloalkyl; and
R^{14} and R^{15} are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^{14} and R^{15} is not more than 4.

Preferred β_2-adrenoreceptor agonists disclosed in WO 02/066422 include:
3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl}amino)hexyl]oxy}butyl)benzenesulfonamide and
3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)benzenesulfonamide.

A preferred β_2-adrenoreceptor agonist disclosed in WO 03/024439 is:
4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol.

A combination of a compound of formula (I) or salt together with an anti-histamine is preferably for oral administration (e.g. as a combined composition such as a combined tablet), and can be for treatment and/or prophylaxis of allergic rhinitis. Examples of anti-histamines include methapyrilene, or H1 antagonists such as cetirizine, loratadine (e.g. Clarityn TM), desloratadine (e.g. Clarinex TM) or fexofenadine (e.g. Allegra TM).

The invention also provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anticholinergic compound, e.g. a muscarinic (M) receptor antagonist in particular an M_1, M_2, M_1/M_2, or M_3 receptor antagonist, more preferably a M_3 receptor antagonist, still more preferably a M_3 receptor antagonist which selectively antagonises (e.g. antagonises 10 times or more strongly) the M_3 receptor over the M_1 and/or M_2 receptor. For combinations of anticholinergic compounds / muscarinic (M) receptor antagonists with PDE4 inhibitors, see for example WO 03/011274 A2 and WO 02/069945 A2 / US 2002/0193393 A1 and US 2002/052312 A1, and some or all of these publications give examples of anticholinergic compounds / muscarinic receptor antagonists which may be used with the compounds of formula (I) or salts, and/or suitable pharmaceutical compositions. For example, the muscarinic receptor antagonist can comprise or be an ipratropium salt (e.g. ipratropium bromide), an oxitropium salt (e.g. oxitropium bromide), or more preferably a tiotropium salt (e.g. tiotropium bromide); see e.g. EP 418 716 A1 for tiotropium.

The anticholinergic compound or muscarinic (M) receptor antagonist, e.g. M_3 receptor antagonist, is preferably for inhaled administration, more preferably in particle-size-reduced form e.g. as defined herein. More preferably, both the muscarinic (M) receptor antagonist and the compound of formula (I) or the pharmaceutically acceptable salt thereof are for inhaled administration. Preferably, the anticholinergic compound or muscarinic receptor antagonist and the compound of formula (I) or salt are for simultaneous administration. The muscarinic receptor antagonist combination is preferably for treatment and/or prophylaxis of COPD.

Other suitable combinations include, for example, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with another anti-inflammatory agent such as an anti-inflammatory corticosteroid; or a non-steroidal anti-inflammatory drug (NSAID) such as a leukotriene antagonist (e.g. montelukast), an iNOS inhibitor, a tryptase inhibitor, an elastase inhibitor, a beta-2 integrin antagonist, an adenosine 2a agonist, a CCR3 antagonist, or a 5-lipoxogenase inhibitor; or an antiinfective agent (eg. an antibiotic or an antiviral). An iNOS inhibitor is preferably for

oral administration. Suitable iNOS inhibitors (inducible nitric oxide synthase inhibitors) include those disclosed in WO 93/13055, WO 98/30537, WO 02/50021, WO 95/34534 and WO 99/62875. Suitable CCR3 inhibitors include those disclosed in WO 02/26722.

In a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anti-inflammatory corticosteroid (which is preferably for treatment and/or prophylaxis of asthma, COPD or allergic rhinitis), then preferably the anti-inflammatory corticosteroid is fluticasone, fluticasone propionate (e.g. see US patent 4,335,121), beclomethasone, beclomethasone 17-propionate ester, beclomethasone 17,21-dipropionate ester, dexamethasone or an ester thereof, mometasone or an ester thereof, ciclesonide, budesonide, flunisolide, or a compound as described in WO 02/12266 A1 (e.g. as claimed in any of claims 1 to 22 therein), or a pharmaceutically acceptable salt of any of the above. If the anti-inflammatory corticosteroid is a compound as described in WO 02/12266 A1, then preferably it is Example 1 therein {which is 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester} or Example 41 therein {which is 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester}, or a pharmaceutically acceptable salt thereof. The anti-inflammatory corticosteroid is preferably for intranasal or inhaled administration. Fluticasone propionate is preferred and is preferably for inhaled administration to a human either (a) at a dose of 250 micrograms once per day or (b) at a dose of 50 to 250 micrograms twice per day.

Also provided is a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with β_2-adrenoreceptor agonist and an anti-inflammatory corticosteroid, for example as described in WO 03/030939 A1. Preferably this combination is for treatment and/or prophylaxis of asthma, COPD or allergic rhinitis. The β_2-adrenoreceptor agonist and/or the anti-inflammatory corticosteroid can be as described above and/or as described in WO 03/030939 A1. Most preferably, in this "triple" combination, the β_2-adrenoreceptor agonist is salmeterol or a pharmaceutically acceptable salt thereof (e.g. salmeterol xinafoate) and the anti-inflammatory corticosteroid is fluticasone propionate.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus a pharmaceutical composition comprising a combination as defined above together with one or more pharmaceutically acceptable carriers and/or excipients represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical composition(s).

In one embodiment, the combination as defined herein can be for simultaneous inhaled administration and is disposed in a combination inhalation device. Such a combination

inhalation device is another aspect of the invention. Such a combination inhalation device can comprise a combined pharmaceutical composition for simultaneous inhaled administration (e.g. dry powder composition), the composition comprising all the individual compounds of the combination, and the composition being incorporated into a plurality of sealed dose containers mounted longitudinally in a strip or ribbon inside the inhalation device, the containers being rupturable or peel-openable on demand; for example such inhalation device can be substantially as described in GB 2,242,134 A (DISKUS ^{TM}) and/or as described above. Alternatively, the combination inhalation device can be such that the individual compounds of the combination are administrable simultaneously but are stored separately (or wholly or partly stored separately for triple combinations), e.g. in separate pharmaceutical compositions, for example as described in PCT/EP03/00598 filed on 22 January 2003 (e.g. as described in the claims thereof e.g. claim 1).

The invention also provides a method of preparing a combination as defined herein, the method comprising either

(a) preparing a separate pharmaceutical composition for administration of the individual compounds of the combination either sequentially or simultaneously, or

(b) preparing a combined pharmaceutical composition for administration of the individual compounds of the combination simultaneously,

wherein the pharmaceutical composition comprises the combination together with one or more pharmaceutically acceptable carriers and/or excipients.

The invention also provides a combination as defined herein, prepared by a method as defined herein.

Biological Test Methods

PDE 3, PDE 4B, PDE 4D, PDE 5, PDE 6 Primary assay methods

The activity of the compounds can be measured in the assay methods shown below. Preferred compounds of the invention are selective PDE4 inhibitors, i.e. they inhibit PDE4 (e.g. PDE4B and/or PDE4D, preferably PDE4B) more strongly than they inhibit PDE3 and/or more strongly than they inhibit PDE5 and/or more strongly than they inhibit PDE6.

PDE enzyme sources and literature references

Human recombinant PDE4B, in particular the 2B splice variant thereof (HSPDE4B2B), is disclosed in WO 94/20079 and also M.M. McLaughlin et al., "A low *K*m, rolipram-sensitive, cAMP-specific phosphodiesterase from human brain: cloning and expression of cDNA, biochemical characterisation of recombinant protein, and tissue distribution of mRNA", *J. Biol. Chem.*, 1993, **268**, 6470-6476. Human recombinant PDE4B was expressed in the PDE-deficient yeast *Saccharomyces cerevisiae* strain GL62. 100,000 x *g* supernatant fractions of yeast cell lysates were used for PDE4B assays and inhibitor studies.

Human recombinant PDE4D (HSPDE4D3A) is disclosed in P. A. Baecker et al., "Isolation of a cDNA encoding a human rolipram-sensitive cyclic AMP phoshodiesterase (PDE IV_D)", *Gene*, 1994, **138**, 253-256.

Human recombinant PDE5 is disclosed in K. Loughney et al., "Isolation and characterisation of cDNAs encoding PDE5A, a human cGMP-binding, cGMP-specific 3',5'-cyclic nucleotide phosphodiesterase", *Gene*, 1998, **216**, 139-147.

PDE3 was purified from bovine aorta as described by H. Coste and P. Grondin, "Characterisation of a novel potent and specific inhibitor of type V phosphodiesterase", *Biochem. Pharmacol.*, 1995, **50**, 1577-1585.

PDE6 was purified from bovine retina as described by: P. Catty and P. Deterre, "Activation and solubilization of the retinal cGMP-specific phosphodiesterase by limited proteolysis", *Eur. J. Biochem.*, 1991, **199**, 263-269; A. Tar et al. "Purification of bovine retinal cGMP phosphodiesterase", *Methods in Enzymology*, 1994, **238**, 3-12; and/or D. Srivastava et al. "Effects of magnesium on cyclic GMP hydrolysis by the bovine retinal rod cyclic GMP phosphodiesterase", *Biochem. J.*, 1995, **308**, 653-658.

Inhibition of PDE 3, PDE 4B, PDE 4D, PDE 5 or PDE 6 activity: radioactive Scintillation Proximity Assay (SPA)

The ability of compounds to inhibit catalytic activity at PDE4B or 4D (human recombinant), PDE3 (from bovine aorta) or PDE5 (human recombinant) or PDE6 (from bovine retina) was determined by Scintillation Proximity Assay (SPA) in 96-well format. Test compounds (preferably as a solution in DMSO, e.g. about 2 microlitre (ul) volume of DMSO solution) were preincubated at ambient temperature (room temperature, e.g. 19-23°C) in Wallac Isoplates (code 1450-514) with PDE enzyme in 50mM Tris-HCl buffer pH 7.5 , 8.3mM $MgCl_2$, 1.7mM EGTA, 0.05% (w/v) bovine serum albumin for 10-30 minutes (usually 30 minutes). The enzyme concentration was adjusted so that no more than 20% hydrolysis of the substrate defined below occurred in control wells without compound, during the incubation. For PDE3, PDE4B and PDE4D assays, [5',8-^{3}H]Adenosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech , code TRK.559; or Amersham Biosciences UK Ltd, Pollards Wood, Chalfont St Giles, Buckinghamshire HP8 4SP, UK) was added to give 0.05uCi per well and ~ 10nM final concentration. For the PDE5 and PDE6 assay [8-^{3}H]Guanosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech , code TRK.392) was added to give 0.05uCi per well and ~ 36nM final concentration. Plates, preferably containing approx. 100 ul volume of assay mixture, were mixed on an orbital shaker for 5 minutes and incubated at ambient temperature for 1 hour. Phosphodiesterase SPA beads (Amersham Pharmacia Biotech, code RPNQ 0150) were added (~1mg per well) to terminate the assay. Plates were sealed and shaken and allowed to stand at ambient temperature for 35 minutes to 1 hour (preferably 35 minutes) to allow the beads to settle. Bound radioactive product was measured using a WALLAC TRILUX 1450 Microbeta scintillation counter. For inhibition curves, 10 concentrations (1.5–M - 30uM) of each compound were assayed. Curves were analysed using ActivityBase and XLfit (ID Businesss Solutions Limited, 2 Ocean Court, Surrey Research Park, Guildford, Surrey GU2 7QB, United Kindgom) Results were expressed as pIC_{50} values.

In an alternative to the above radioactive SPA assay, PDE4B or PDE4D inhibition can be measured in the following Fluorescence Polarisation (FP) assay:

Inhibition of PDE4B or PDE4D activity: Fluorescence Polarisation (FP) assay

The ability of compounds to inhibit catalytic activity at PDE4B (human recombinant) or PDE4D (human recombinant) was determined by IMAP Fluorescence Polarisation (FP) assay (IMAP Explorer kit, available from Molecular Devices Corporation, Sunnydale, CA, USA; Molecular Devices code: R8062) in 384-well format. The IMAP FP assay is able to measure PDE activity in an homogenous, non-radioactive assay format. The FP assay uses the ability of immobilised trivalent metal cations, coated onto nanoparticles (tiny beads), to bind the phosphate group of Fl-AMP that is produced on the hydrolysis of fluorescein-labelled (Fl) cyclic adenosine mono-phosphate (Fl-cAMP) to the non-cyclic Fl-AMP form. Fl-cAMP does not bind. Binding of Fl-AMP product to the beads (coated with the immobilised trivalent cations) slows the rotation of the bound Fl-AMP and leads to an increase in the fluorescence polarisation ratio of parallel to perpendicular light. Inhibition of the PDE reduces/inhibits this signal increase.

Test compounds (small volume, e.g. ca. 0.5 to 1 ul, preferably ca. 0.5 ul, of solution in DMSO) were preincubated at ambient temperature (room temperature, e.g. 19-23°C) in black 384-well microtitre plates (supplier: NUNC, code 262260) with PDE enzyme in 10mM Tris-HCl buffer pH 7.2, 10mM $MgCl_2$, 0.1% (w/v) bovine serum albumin, and 0.05% NaN_3 for 10-30 minutes. The enzyme level was set by experimentation so that reaction was linear throughout the incubation. Fluorescein adenosine 3',5'-cyclic phosphate (from Molecular Devices Corporation, Molecular Devices code: R7091) was added to give about 40nM final concentration (final assay volume usually ca. 20-40 ul, preferably ca. 20 ul). Plates were mixed on an orbital shaker for 10 seconds and incubated at ambient temperature for 40 minutes. IMAP binding reagent (as described above, from Molecular Devices Corporation, Molecular Devices code: R7207) was added (60ul of a 1 in 400 dilution in binding buffer of the kit stock solution) to terminate the assay. Plates were allowed to stand at ambient temperature for 1 hour. The Fluorescence Polarisation (FP) ratio of parallel to perpendicular light was measured using an Analyst^{TM} plate reader (from Molecular Devices Corporation). For inhibition curves, 10 concentrations (1.5nM - 30uM) of each compound were assayed. Curves were analysed using ActivityBase and XLfit (ID Businesss Solutions Limited, 2 Ocean Court, Surrey Research Park, Guildford, Surrey GU2 7QB, United Kindgom). Results were expressed as pIC_{50} values.

In the FP assay, all reagents were dispensed using Multidrop^{TM} (available from Thermo Labsystems Oy, Ratastie 2, PO Box 100, Vantaa 01620, Finland).

For a given PDE4 inhibitor, the PDE4B (or PDE4D) inhibition values measured using the SPA and FP assays can differ slightly. However, in a regression analysis of 100 test compounds, the pIC_{50} inhibition values measured using SPA and FP assays have been found generally to agree within 0.5 log units, for PDE4B and PDE4D (linear regression coefficient 0.966 for PDE4B and 0.971 for PDE4D; David R.Mobbs et al., "Comparison of the IMAP Fluorescence Polarisation Assay with the Scintillation Proximity Assay for Phosphodiesterase Activity", poster to be presented at 2003 Molecular Devices UK & Europe User Meeting, 2nd October 2003, Down Hall, Harlow, Essex, United Kingdom).

Biological Data obtained for some of the Examples (PDE4B inhibitory activity, either as one reading or as an average of ca. 2-6 readings) are as follows, based on current measurements only. In each of the SPA and FP assays, absolute accuracy of measurement is not possible, and the readings given are accurate only up to about ± 0.5 of a log unit, depending on the number of readings made and averaged:

Example number	**PDE4B pIC_{50}** (± about 0.5)
6	8.1
10	8.2
12	7.9
14	7.6

23	8.1
24	8.2
35	7.5
42	8.3
7, 43, 48, 60, 61 and 64	6.6 to 7.2
2, 17, 26, 34, 38, 39, 44, 50, 59, 62, 63, 66, 71, 76, 77 and 84	7.5 to 9.1

Many, but not all, of the Examples have been tested for PDE4B inhibition. Of the Examples tested for PDE4B inhibition, some were tested by the radioactive SPA assay, some were tested by the FP assay.

Most or substantially all of Examples 1-45, 47-55, 57-81, 83 and 84 have PDE4B inhibitory activities in the range of pIC_{50} = about 6 (± about 0.5) to about 9.1 (± 0.5).

The Examples wherein R^3 = cyclohexyl (NHR^3 or NR^3R^{3a} = sub-formula (c)), tetrahydro-2H-pyran-4-yl (NHR^3 or NR^3R^{3a} = group (h)), or certain other types of substituted cyclohexyl or certain heterocycles, or Examples wherein NHR^3 or NR^3R^{3a} = sub-formula (s), usually or often (based on data for R^1 = ethyl) have a higher level of selectivity for PDE4B over PDE5, as measured in the above enzyme inhibition assays, compared to the selectivities of comparable Examples wherein R^3 = cyclopropyl (NHR^3 or NR^3R^{3a} = sub-formula (b)).

Emesis: Some known PDE4 inhibitors can cause emesis and/or nausea to greater or lesser extents (e.g. see Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438, see especially pages 433-434 and refs cited therein). Therefore, it would be preferable, but <u>not</u> essential, if a particular PDE4 inhibitory compound or salt of the invention were to cause only limited or manageable emetic side-effects. Emetic side-effects can for example be measured by the emetogenic potential of the compound or salt when administered to ferrets; for example one can measure the time to onset, extent, frequency and/or duration of vomiting, retching and/or writhing in ferrets after oral or parenteral administration of the compound or salt. See for example In vivo Assay 4 hereinafter for a measurement method for anti-inflammatory effect, emetic side-effects and therapeutic index (TI) in the ferret. See also for example A. Robichaud et al., "Emesis induced by inhibitors of [PDE IV] in the ferret", *Neuropharmacology*, 1999, 38, 289-297, erratum *Neuropharmacology*, 2001, 40, 465-465. However, optionally, emetic side-effects and therapeutic index (TI) in rats can be conveniently measured by monitoring the pica feeding behaviour of rats after administration of the compound or salt of the invention (see In Vivo Assay 2 below).

Other side effects: Some known PDE4 inhibitors can cause other side effects such as headache and other central nervous sytem (CNS-) mediated side effects; and/or gastrointestinal (GI) tract disturbances. Therefore, it would be preferable but not essential if a particular PDE4 inhibitory compound or salt of the invention were to cause only limited or manageable side-effects in one or more of these side-effect categories.

***In Vivo* Biological Assays**

The *in vitro* enzymatic PDE4B inhibition assay described above should be regarded as being the primary test of biological activity. However, additional *in vivo* biological tests, which are optional and which are not an essential measure of efficacy or side-effects, are described below.

In Vivo Assay 1. LPS-induced pulmonary neutrophilia in rats: effect of orally administered PDE4 inhibitors

Pulmonary neutrophil influx has been shown to be a significant component to the family of pulmonary diseases like chronic obstructive pulmonary disease (COPD) which can involve chronic bronchitis and/or emphysema (G.F. Filley, *Chest.* 2000; 117(5); 251s-260s). The purpose of this neutrophilia model is to study the potentially anti-inflammatory effects *in vivo* of orally administered PDE4 inhibitors on neutrophilia induced by inhalation of aerosolized lipopolysaccharide (LPS), modelling the neutrophil inflammatory component(s) of COPD. See the literature section below for scientific background.

Male Lewis rats (Charles River, Raleigh, NC, USA) weighing approximately 300-400 grams are pretreated with either (a) test compound suspended in 0.5% methylcellulose (obtainable from Sigma-Aldrich, St Louis, MO, USA) in water or (b) vehicle only, delivered orally in a dose volume of 10 ml/kg. Generally, dose response curves are generated using the following doses of PDE4 inhibitors: 10.0, 2.0, 0.4, 0.08 and 0.016 mg/kg. Thirty minutes following pretreatment, the rats are exposed to aerosolized LPS (Serotype E. Coli 026:B6 prepared by trichloroacetic acid extraction, obtainable from Sigma-Aldrich, St Louis, MO, USA), generated from a nebulizer containing a 100 μg/ml LPS solution. Rats are exposed to the LPS aerosol at a rate of 4 L/min for 20 minutes. LPS exposure is carried out in a closed chamber with internal dimensions of 45 cm length x 24 cm width x 20 cm height. The nebulizer and exposure chamber are contained in a certified fume hood. At 4 hours-post LPS exposure the rats are euthanized by overdose with pentobarbital at 90 mg/kg, administered intraperitoneally. Bronchoalveolar lavage (BAL) is performed through a 14 gauge blunt needle into the exposed trachea. Five, 5 ml washes are performed to collect a total of 25 ml of BAL fluid. Total cell counts and leukocyte differentials are performed on BAL fluid in order to calculate neutrophil influx into the lung. Percent neutrophil inhibition at each dose (cf. vehicle) is calculated and a variable slope, sigmoidal dose-response curve is generated, usually using Prism Graph-Pad. The dose-response curve is used to calculate an ED50 value (in mg per kg of body weight) for inhibition by the PDE4 inhibitor of the LPS-induced neutrophilia.

Results: Based on current measurements, the compounds of Examples 14, 17, 23, 35 and 38, administered orally in the above procedure, exhibited neutrophilia-inhibition ED50 values in the range of about 0.03 mg/kg to about 1 mg/kg, subject to testing inaccuracies.

Alternative method and results: In an alternative embodiment of the procedure, a single oral dose of 10 mg/kg or 1 mg/kg of the PDE4 inhibitor (or vehicle) is administered to the rats, and percent neutrophil inhibition is calculated and reported for that specific dose. In this embodiment, based on current measurements, the compounds of Examples 2, 14, 23 and 38, administered orally in this alternative procedure at a single dose of 10 mg/kg, exhibited percent neutrophilia-inhibition in the range of about 74% to about 86%, subject to testing inaccuracies.

Literature:

Filley G.F. Comparison of the structural and inflammatory features of COPD and asthma. *Chest.* 2000; 117(5) 251s-260s.

Howell RE, Jenkins LP, Fielding LE, and Grimes D. Inhibition of antigen-induced pulmonary eosinophilia and neutrophilia by selective inhibitors of phosphodiesterase types 3 and 4 in brown Norway rats. *Pulmonary Pharmacology.* 1995; 8: 83-89.

Spond J, Chapman R, Fine J, Jones H, Kreutner W, Kung TT, Minnicozzi M. Comparison of PDE 4 inhibitors, Rolipram and SB 207499 (Ariflo™), in a rat model of pulmonary neutrophilia. *Pulmonary Pharmacology and Therapeutics.* 2001; 14: 157-164.

Underwood DC, Osborn RR, Bochnowicz S, Webb EF, Rieman DJ, Lee JC, Romanic AM, Adams JL, Hay DWP, and Griswold DE. SB 239063, a p38 MAPK inhibitor, reduces neutrophilia, inflammatory cytokines, MMP-9, and fibrosis in lung. *Am J Physiol Lung Cell Mol Physiol.* 2000; 279: L895-L902.

In Vivo Assay 2. Rat Pica Model of emesis

Background: Selective PDE4 inhibitors have been shown to inhibit inflammation in various *in vitro* and *in vivo* models by increasing intracellular levels of cAMP of many immune cells (e.g. lymphocytes, monocytes). However, a side effect of some PDE4 inhibitors in many species is emesis. Because many rat models of inflammation are well characterized, they have been used in procedures (see e.g. In Vivo Assay 1 above) to show beneficial anti-inflammatory effects of PDE 4 inhibitors. However rats have no emetic response (they have no vomit reflex), so that the relationship between beneficial anti-inflammatory effects of PDE 4 inhibitors and emesis is difficult to study directly in rats.

However, in 1991, Takeda *et al.* (see Literature section below) demonstrated that the pica feeding response is analogous to emesis in rats. Pica feeding is a behavioural response to illness in rats wherein rats eat non-nutritive substances such as earth or in particular clay (e.g. kaolin) which may help to absorb toxins. Pica feeding can be induced by motion and chemicals (especially chemicals which are emetic in humans), and can be inhibited pharmacologically with drugs that inhibit emesis in humans. The Rat Pica Model, In Vivo Assay 2, can determine the level of pica response of rats to PDE 4 inhibition at pharmacologically relevant doses in parallel to *in vivo* anti-inflammatory Assays in (a separate set of) rats (e.g. In Vivo Assay 1 above). Anti-inflammatory and pica assays in the same species together can provide data on the "therapeutic index" (TI) in the rat of the compounds/salts of the invention. The Rat TI can for example be

calculated as the ratio of a) the potentially-emetic Pica Response ED50 dose from Assay 2 to b) the rat anti-inflammatory ED50 dose (e.g. measured by rat neutrophilia-inhibition in eg In Vivo Assay 1), with larger TI ratios possibly indicating lower emesis at many anti-inflammatory doses. This might allow a choice of a non-emetic or minimal-emetic pharmaceutical dose of the compounds or salts of the invention which has an anti-inflammatory effect. It is recognised however that achieving a low-emetic PDE4 inhibitory compound is not essential to the invention.

Procedure: On the first day of the experiment, the rats are housed individually in cages without bedding or "enrichment". The rats are kept off of the cage floor by a wire screen. Pre-weighed food cups containing standard rat chow and clay pellets are placed in the cage. The clay pellets, obtainable from Languna Clay Co, City of Industry, CA, USA, are the same size and shape as the food pellets. The rats are acclimated to the clay for 72 hours, during which time the cups and food and clay debris from the cage are weighed daily on an electronic balance capable of measuring to the nearest 0.1 grams. By the end of the 72 hour acclimation period the rats generally show no interest in the clay pellets.

At the end of 72 hours the rats are placed in clean cages and the food cups weighed. Rats that are still consuming clay regularly are removed from the study. Immediately prior to the dark cycle (the time when the animals are active and should be eating) the animals are split into treatment groups and dosed orally with a dose of the compound/salt of the invention (different doses for different treatment groups) or with vehicle alone, at a dose volume of 2 ml/kg. In this oral dosing, the compound/salt is in the form of a suspension in 0.5% methylcellulose (obtainable Sigma-Aldrich, St. Louis, MO, USA) in water. The food and clay cups and cage debris are weighed the following day and the total clay and food consumed that night by each individual animal is calculated.

A dose response is calculated by first converting the data into quantal response, where animals are either positive or negative for the pica response. A rat is "pica positive" if it consumes greater than or equal to 0.3 grams of clay over the mean of is usually calculated using logistic regression performed by the Statistica software statistical package. A Pica Response ED50 value in mg per kg of body weight can then be calculated.

The Pica Response ED50 value can be compared to the neutrophilia-inhibition ED50 values for the same compound administered orally to the rat (measurable by In Vivo Assay 1 above), so that a Therapeutic Index (TI) in rats can be calculated thus:

$$\text{Rat Therapeutic index (TI) (50/50)} = \frac{\text{Pica Response ED50 value}}{\text{rat neutrophilia-inhibition ED50 value}}$$

In general, the Therapeutic Index (TI) calculated this way is often substantially different to, for example can often be substantially higher than, the TI (D20/D50) calculated in the ferret (see In vivo Assay 4 below).

Results: Using the above procedure, and according to current measurements, the compounds of Examples 14, 17, 23, 35 and 38 exhibited a Pica Response ED50 in the range of about 2 mg/kg to greater than about 50 mg/kg, subject to testing inaccuracies. Taking the specific Pica Response ED50 values for these compounds together with the specific rat neutrophilia-inhibition ED50 values measured in In Vivo Assay 1 for Examples 14, 17, 23, 35 and 38, the Rat Therapeutic Index (TI) for orally-administered

Examples 14, 17, 23, 35 and 38 was calculated using the above equation as being in the range of from about 12 to about 470, according to current measurements, subject to testing inaccuracies.

Literature:

Beavo JA, Contini, M., Heaslip, R.J. Multiple cyclic nucleotide phosphodiesterases. *Mol Pharmacol.* 1994; 46:399-405.

Spond J, Chapman R, Fine J, Jones H, Kreutner W, Kung TT, Minnicozzi M. Comparison of PDE 4 inhibitors, Rolipram and SB 207499 (Ariflo™), in a rat model of pulmonary neutrophilia. *Pulmonary Pharmacology and Therapeudtics.* 2001; 14:157-164.

Takeda N, Hasegawa S, Morita M, and Matsunaga T. Pica in rats is analogous to emesis: an animal model in emesis research. *Pharmacology, Biochemistry and Behavior.* 1991; 45:817-821.

Takeda N, Hasegawa S, Morita M, Horii A, Uno A, Yamatodani A and Matsunaga T. Neuropharmacological mechanisms of emesis. I . Effects of antiemetic drugs on motion- and apomorphine-induced pica in rats. *Meth Find Exp Clin Pharmacol.* 1995; 17(9) 589-596.

Takeda N, Hasegawa S, Morita M, Horii A, Uno A, Yamatodani A and Matsunaga T. Neuropharmacological mechanisms of emesis. II . Effects of antiemetic drugs on cisplatin-induced pica in rats. *Meth Find Exp Clin Pharmacol.* 1995; 17(9) 647-652.

In Vivo Assay 3. LPS induced pulmonary neutrophilia in rats: effect of intratracheally administered PDE4 inhibitors

This assay is an animal model of inflammation in the lung – specifically neutrophilia induced by lipopolysaccharide (LPS) – and allows the study of putative inhibition of such neutrophilia (anti-inflammatory effect) by intratracheally (i.t.) administered PDE4 inhibitors. The PDE4 inhibitors are preferably in dry powder or wet suspension form. I.t. administration is one model of inhaled administration, allowing topical delivery to the lung.

Animals: Male CD (Sprague Dawley Derived) rats supplied by Charles River, Raleigh, NC, USA are housed in groups of 5 rats per cage, acclimatised after delivery for at least 7 days with bedding/nesting material regularly changed, fed on SDS diet R1 pelleted food given *ad lib,* and supplied with daily-changed pasteurised animal grade drinking water.

Device for dry powder administration: Disposable 3-way tap between dosing needle and syringe. A 3-way sterile tap (Vycon Ref 876.00) is weighed, the drug blend or inhalation grade lactose (vehicle control) is then added to the tap, the tap closed to prevent loss of drug, and the tap is re-weighed to determine the weight of drug in the tap. After dosing, the tap is weighed again to determine the weight of drug that had left the tap. The needle, a Sigma Z21934-7 syringe needle 19-gauge 152 mm (6 inches) long with luer hub, is cut by engineering to approximately 132 mm (5.2 inches), a blunt end is

made to prevent them damaging the rat's trachea, and the needle is weighed prior to and after drug delivery to confirm that no drug is retained in the needles after dosing.

Device for wet suspension administration: This is the similar to the above but a blunt dosing needle, whose forward end is slightly angled to the needle axis, is used, with a flexible plastic portex canula inserted into the needle.

Drugs and Materials: Lipopolysaccharide (LPS) (Serotype:0127:B8) (L3129 Lot 61K4075) was dissolved in phosphate-buffered saline (PBS). PDE4 inhibitors are used in size-reduced (e.g. micronised) form, for example according to the Micronisation Example given above. For dry powder administration of the drug, the Dry Powder Formulation Example given above, comprising drug and inhalation-grade lactose, can be used. The inhalation-grade lactose usually used (Lot E98L4675 Batch 845120) has 10% fines (10% of material under 15um particle size measured by Malvern particle size).

Wet suspensions of the drug can be prepared by added the required volume of vehicle to the drug, the vehicle being used being a mixture of saline/tween (0.2% tween 80). The wet suspension was sonicated for 10 minutes prior to use.

Preparation, and dosing with PDE 4 inhibitor: Rats are anaesthetised by placing the animals in a sealed Perspex chamber and exposing them to a gaseous mixture of isoflourane (4.5 %), nitrous oxide (3 litres.minute^{-1}) and oxygen (1 litre.minute^{-1}). Once anaesthetised, the animals are placed onto a stainless steel i.t. dosing support table. They are positioned on their back at approximately a 35° angle. A light is angled against the outside of the throat to highlight the trachea. The mouth is opened and the opening of the upper airway visualised. The procedure varies for wet suspension and dry powder administration of PDE4 inhibitors as follows:

Dosing with a Wet suspension: A portex cannula is introduced via a blunt metal dosing needle that had been carefully inserted into the rat trachea. The animals are intratracheally dosed with vehicle or PDE4 inhibitor via the dosing needle with a new internal canula used for each different drug group. The formulation is slowly (10 seconds) dosed into the trachea using a syringe attached to the dosing needle.

Dosing with a Dry Powder: The three-way tap device and needle are inserted into the rat trachea up to a pre-determined point established to be located approximately 1 cm above the primary bifurcation. Another operator holds the needle at the specified position whilst 2x 4ml of air is delivered through the three-way tap by depressing the syringes (ideally coinciding with the animal inspiring), aiming to expel the entire drug quantity from the tap. After dosing, the needle and tap are removed from the airway and the tap is closed off to prevent any retained drug leaving the tap.

After dosing with either wet suspension or dry powder, the animals are then removed from the table and observed constantly until they have recovered from the effects of anaesthesia. The animals are returned to the holding cages and given free access to food and water; they are observed and any unusual behavioural changes noted.

Exposure to LPS: About 2 hours after i.t. dosing with vehicle control or the PDE4 inhibitor, the rats are placed into sealed Perspex containers and exposed to an aerosol of LPS (nebuliser concentration 150 μg.ml^{-1}) for 15 minutes. Aerosols of LPS are generated by a nebuliser (DeVilbiss, USA) and this is directed into the Perspex exposure chamber.

Following the 15-minute LPS-exposure period, the animals are returned to the holding cages and allowed free access to both food and water.

[In an alternative embodiment, the rats can exposed to LPS less than 2 hours after i.t. dosing. In another alternative embodiment, the rats can exposed to LPS more than 2 hours (e.g. ca. 4 or ca. 6 hours) after i.t. dosing by vehicle or PDE4 inhibitor, to test whether or not the PDE4 inhibitor has a long duration of action (which is not essential).]

Bronchoalveolar lavage: 4 hours after LPS exposure the animals are killed by overdose of sodium pentobarbitone (i.p.). The trachea is cannulated with polypropylene tubing and the lungs lavaged (washed out) with 3 x 5 mls of heparinised (25 units.ml^{-1}) phosphate buffered saline (PBS).

Neutrophil cell counts: The Bronchoalveolar lavage (BAL) samples are centrifuged at 1300 rpm for 7 minutes. The supernatant is removed and the resulting cell pellet resuspended in 1 ml PBS. A cell slide of the resuspension fluid is prepared by placing 100µl of resuspended BAL fluid into cytospin holders and then spun at 5000 rpm for 5 minutes. The slides are allowed to air dry and then stained with Leishmans stain (20 minutes) to allow differential cell counting. The total cells are also counted from the resuspension. From these two counts, the total numbers of neutrophils in the BAL are determined. For a measure of PDE4-inhibitor-induced inhibition of neutrophilia, a comparison of the neutrophil count in rats treated with vehicle and rats treated with PDE4 inhibitors is conducted.

By varying the dose of the PDE4 inhibitor used in the dosing step (e.g. 0.2 or 0.1 mg of PDE4 inhibitor per kg of body weight, down to e.g. 0.01 mg/kg), a dose-response curve can be generated.

In vivo Assay 4. Evaluation of Therapeutic Index of Orally-administered PDE 4 inhibitors in the conscious ferret

1.1 Materials

The following materials are used for these studies:

PDE4 inhibitors are prepared for oral (p.o.) administration by dissolving in a fixed volume (1 ml) of acetone and then adding cremophor to 20% of the final volume. Acetone is evaporated by directing a flow of nitrogen gas onto the solution. Once the acetone is removed, the solution is made up to final volume with distilled water.
LPS is dissolved in phosphate buffered saline.

1.2 Animals

Male ferrets (Mustela Pulorius Furo, weighing 1 – 2 kg) are transported and allowed to acclimatise for not less than 7 days. The diet comprises SDS diet C pelleted food given *ad lib* with Whiskers^{TM} cat food given 3 times per week. The animals are supplied with pasteurised animal grade drinking water changed daily.

1.3 Experimental Protocol(s)

1.3.1 Dosing with PDE4 inhibitors

PDE4 inhibitors are administered orally (p.o.), using a dose volume of 1ml/kg.

Ferrets are fasted overnight but allowed free access to water. The animals are orally dosed with vehicle or PDE 4 inhibitor using a 15cm dosing needle that is passed down the back of the throat into the oesophagus. After dosing, the animals are returned to holding cages fitted with perspex doors to allow observation, and given free access to water. The animals are constantly observed and any emetic episodes (retching and vomiting) or behavioural changes are recorded. The animals are allowed access to food 60 – 90 minutes after p.o. dosing.

1.3.2 Exposure to LPS

Thirty minutes after oral dosing with compound or vehicle control, the ferrets are placed into sealed perspex containers and exposed to an aerosol of LPS (30 μg/ml) for 10 minutes. Aerosols of LPS are generated by a nebuliser (DeVilbiss, USA) and this is directed into the perspex exposure chamber. Following a 10-minute exposure period, the animals are returned to the holding cages and allowed free access to water, and at a later stage, food. General observation of the animals continues for a period of at least 2.5 hours post oral dosing. All emetic episodes and behavioural changes are recorded.

1.3.3 Bronchoalveolar lavage and cell counts

Six hours after LPS exposure the animals are killed by overdose of sodium pentobarbitone administered intraperitoneally. The trachea is then cannulated with polypropylene tubing and the lungs lavaged twice with 20 ml heparinised (10 units/ml) phosphate buffered saline (PBS). The bronchoalveolar lavage (BAL) samples are centrifuged at 1300 rpm for 7 minutes. The supernatant is removed and the resulting cell pellet re-suspended in 1 ml PBS. A cell smear of re-suspended fluid is prepared and stained with Leishmans stain to allow differential cell counting. A total cell count is made using the remaining re-suspended sample. From this, the total number of neutrophils in the BAL sample is determined.

1.3.4 Pharmacodynamic readouts

The following parameters are recorded:

a) % inhibition of LPS-induced pulmonary neutrophilia to determine the dose of PDE4 inhibitor which gives 50% inhibition (D50).

b) Emetic episodes – the number of vomits and retches are counted to determine the dose of PDE4 inhibitor that gives a 20% incidence of emesis (D20).

c) A therapeutic index (TI), using this assay, is then calculated for each PDE4 inhibitor using the following equation:

$$\text{Ferret Therapeutic Index (TI) (D20/D50)} = \frac{\text{D20 incidence of emesis in ferret}}{\text{D50 inhibition of neutrophilia in ferret}}$$

It is noted that the Ferret Therapeutic index (TI) (D20/D50) calculated using this in vivo Assay 4 is often substantially different to, and for example is often substantially lower than, the Rat TI (50/50) calculated using the rat oral inflammation and pica feeding Assays 1+2.

The calculation of TI using the known PDE4 inhibitor roflumilast in this Assay 4 is:

D20 for emesis = 0.46 mg/kg p.o., D50 for ferret neutroplilia = 0.42 mg/kg p.o., Ferret TI = 1.1.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

EXAMPLES

The various aspects of the invention will now be described by reference to the following examples. These examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In this section, "Intermediates" represent syntheses of intermediate compounds intended for use in the synthesis of the "Examples".

Abbreviations used herein:

BEMP	2-t-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphazine
CDI	1,1'-carbonyldiimidazole
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
Et_2O	diethyl ether
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
h	hours
HOBT	hydroxybenzotriazole = 1-hydroxybenzotriazole
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HPLC	High performance liquid chromatography
LCMS	liquid chromatography / mass spectroscopy
MeCN	acetonitrile
MeOH	methanol
NMR	nuclear magnetic resonance (in which: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, n H means that n is the number of protons)
DIPEA	N,N-diisopropylethylamine ($^iPr_2NEt$)
SPE	solid phase extraction
TBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
THF	Tetrahydrofuran
T_{RET}	retention time (from LCMS)
TLC	thin layer chromatography
Lawesson's reagent	2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide
Burgess Reagent	(Methoxycarbonylsulphamoyl)triethylammonium hydroxide
Room temperature	= ambient temperature: this is usually in the range of about 15 to about 25 °C or about 20 to about 25 °C.

Machine Methods used herein:

LCMS (liquid chromatography / mass spectroscopy)
Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100-1000 amu.
UV wavelength : 215-330nM
Column : 3.3cm x 4.6mm ID, 3μm ABZ+PLUS
Flow Rate : 3ml/min
Injection Volume : 5μl
Solvent A : 95% acetonitrile + 0.05% formic acid
Solvent B : 0.1% formic acid + 10mMolar ammonium acetate
Gradient : 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min

Mass directed autoprep HPLC
The prep column used was a Supelcosil ABZplus (10cm x 2.12cm) (usually 10cm x 2.12cm x 5 μm).
UV wavelength : 200-320nM
Flow : 20ml/min
Injection Volume: 1ml; or more preferably 0.5 ml
Solvent A : 0.1% formic acid (or 0.1% trifluoroacetic acid)
Solvent B : 95% acetonitrile + 5% of (formic acid or trifluoroacetic acid); or more usually 99.95% acetonitrile + 0.05% of (formic acid or trifluoroacetic acid)
Gradient : 100% A/1min, 100-80% A/9min, 80-1% A/3.5min, 1% A/1.4min, 1-100%A/0.1min

Microwave
The CEM Discover Focused Microwave Synthesis system was used.

Intermediates and Examples

All reagents not detailed in the text below are commercially available from established suppliers such as Sigma-Aldrich. The addresses of the suppliers for some of the starting materials mentioned in the Intermediates and Examples below or the Assays above are as follows:

- ABCR GmbH & CO. KG, P.O. Box 21 01 35, 76151 Karlsruhe, Germany
- Aceto Color Intermediates (catalogue name), Aceto Corporation, One Hollow Lane, Lake Success, NY, 11042-1215, USA
- Acros Organics, A Division of Fisher Scientific Company, 500 American Road, Morris Plains, NJ 07950, USA

- Apin Chemicals Ltd., 82 C Milton Park, Abingdon, Oxon OX14 4RY, United Kingdom
- Apollo Scientific Ltd., Unit 1A, Bingswood Industrial Estate, Whaley Bridge, Derbyshire SK23 7LY, United Kingdom
- Aldrich (catalogue name), Sigma-Aldrich Company Ltd., Dorset, United Kingdom, telephone: +44 1202 733114; Fax: +44 1202 715460; ukcustsv@eurnotes.sial.com; or
- Aldrich (catalogue name), Sigma-Aldrich Corp., P.O. Box 14508, St. Louis, MO 63178-9916, USA; telephone: 314-771-5765; fax: 314-771-5757; custserv@sial.com; or
- Aldrich (catalogue name), Sigma-Aldrich Chemie Gmbh, Munich, Germany; telephone: +49 89 6513 0; Fax: +49 89 6513 1169; deorders@eurnotes.sial.com.
- Alfa Aesar, A Johnson Matthey Company, 30 Bond Street, Ward Hill, MA 01835-8099, USA
- Amersham Biosciences UK Ltd, Pollards Wood, Chalfont St Giles, Buckinghamshire HP8 4SP, United Kingdom
- Array Biopharma Inc., 1885 33rd Street, Boulder, CO 80301, USA
- AstaTech, Inc., 8301 Torresdale Ave., 19C, Philadelphia, PA 19136, USA
- Austin Chemical Company, Inc., 1565 Barclay Blvd., Buffalo Grove, IL 60089, USA
- Avocado Research, Shore Road, Port of Heysham Industrial Park, Heysham Lancashire LA3 2XY, United Kingdom
- Bayer AG, Business Group Basic and Fine Chemicals, D-51368 Leverkusen, Germany
- Berk Univar plc, Berk House, P.O.Box 56, Basing View, Basingstoke, Hants RG21 2E6, United Kingdom
- Butt Park Ltd., Braysdown Works, Peasedown St. John, Bath BA2 8LL, United Kingdom
- Chemical Building Blocks (catalogue name), Ambinter, 46 quai Louis Bleriot, Paris, F-75016, France
- ChemBridge Europe, 4 Clark's Hill Rise, Hampton Wood, Evesham, Worcestershire WR11 6FW, United Kingdom
- ChemService Inc., P.O.Box 3108, West Chester, PA 19381, USA
- Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126, USA
- Dynamit Nobel GmbH, Germany; also available from: Saville Whittle Ltd (UK agents of Dynamit Nobel), Vickers Street, Manchester M40 8EF, United Kingdom
- E. Merck, Germany; or E. Merck (Merck Ltd), Hunter Boulevard, Magna Park, Lutterworth, Leicestershire LE17 4XN, United Kingdom
- Esprit Chemical Company, Esprit Plaza, 7680 Matoaka Road, Sarasota, FL 34243, USA
- Exploratory Library (catalogue name), Ambinter, 46 quai Louis Bleriot, Paris, F-75016, France
- Fluka Chemie AG, Industriestrasse 25, P.O. Box 260, CH-9471 Buchs, Switzerland
- Fluorochem Ltd., Wesley Street, Old Glossop, Derbyshire SK13 7RY, United Kingdom
- ICN Biomedicals, Inc., 3300 Hyland Avenue, Costa Mesa, CA 92626, USA
- Interchim Intermediates (catalogue name), Interchim, 213 Avenue Kennedy, BP 1140, Montlucon, Cedex, 03103, France
- Key Organics Ltd., 3, Highfield Indusrial Estate, Camelford, Cornwall PL32 9QZ, United Kingdom
- Lancaster Synthesis Ltd., Newgate, White Lund, Morecambe, Lancashire LA3 3DY, United Kingdom
- Manchester Organics Ltd., Unit 2, Ashville Industrial Estate, Sutton Weaver, Runcorn, Cheshire WA7 3PF, United Kingdom

- Matrix Scientific, P.O. Box 25067, Columbia, SC 29224-5067, USA
- Maybridge Chemical Company Ltd., Trevillett, Tintagel, Cornwall PL34 0HW, United Kingdom
- Maybridge Reactive Intermediates (catalogue name), Maybridge Chemical Company Ltd., Trevillett, Tintagel, Cornwall PL34 0HW, United Kingdom
- MicroChemistry Building Blocks (catalogue name), MicroChemistry-RadaPharma, Shosse Entusiastov 56, Moscow, 111123, Russia
- Miteni S.p.A., Via Mecenate 90, Milano, 20138, Italy
- Molecular Devices Corporation, Sunnydale, CA, USA
- N.D. Zelinsky Institute, Organic Chemistry, Leninsky prospect 47, 117913 Moscow B-334, Russia
- Optimer Building Block (catalogue name), Array BioPharma, 3200 Walnut Street, Boulder, CO 80301, USA
- Peakdale Molecular Ltd., Peakdale Science Park, Sheffield Road, Chapel-en-le-Frith, High Peak SK23 0PG, United Kingdom
- Pfaltz & Bauer, Inc., 172 East Aurora Street, Waterbury, CT 06708, USA
- Rare Chemicals (catalogue name), Rare Chemicals GmbH, Schulstrasse 6, 24214 Gettorf, Germany
- SALOR (catalogue name) (Sigma Aldrich Library of Rare Chemicals), Aldrich Chemical Company Inc, 1001 West Saint Paul Avenue, Milwaukee, WI 53233, USA
- Sigma (catalogue name), Sigma-Aldrich Corp., P.O. Box 14508, St. Louis, MO 63178-9916, USA; see "Aldrich" above for other non-US addresses and other contact details
- SIGMA-RBI, One Strathmore Road, Natick, MA 01760-1312, USA
- Synchem OHG Heinrich-Plett-Strasse 40, Kassel, D-34132, Germany
- Syngene International Pvt Ltd, Hebbagodi, Hosur Road, Bangalore, India.
- TCI America, 9211 North Harborgate Street, Portland, OR 97203, USA
- TimTec Building Blocks A, TimTec, Inc., P O Box 8941, Newark, DE 19714-8941, USA
- Trans World Chemicals, Inc., 14674 Southlawn Lane, Rockville, MD 20850, USA
- Ubichem PLC, Mayflower Close, Chandlers Ford Industrial Estate, Eastleigh, Hampshire SO53 4AR, United Kingdom
- Ultrafine (UFC Ltd.), Synergy House, Guildhall Close, Manchester Science Park, Manchester M15 6SY, United Kingdom

Table of Intermediates

Intermediate Number	Name
1	Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
2	Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
3	4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
4	N'-Acetyl-4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide

5	4-(Cyclopentylamino)-1-ethyl-N'-[(methylsulfonyl)acetyl]-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide
6	Ethyl 4-(4-fluorophenylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
7	4-(Cyclopentylamino)-1-ethyl-N-[methyl]-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide
8	Methanesulfonyl acetic acid hydrazide
9	Acetamidoxime
10	4-(Cyclopentylamino)-1-ethyl-N'-isobutyryl-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide
11	4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
12	4-Chloro-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridine
13	4-Chloro-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridine
14	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine
15	4-Chloro-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridine
16	Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
17	1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
18	Tert-butyl 2-{[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]carbonyl}hydrazinecarboxylate
19	1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide dihydrochloride
20	N'-(Cyclopropylcarbonyl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide
21	Tetrahydro-2H-pyran-4-amine = 4-Aminotetrahydropyran
21A	Tetrahydro-2H-pyran-4-amine hydrochloride = 4-aminotetrahydropyran hydrochloride
22	N'-Hydroxy-2-methoxyethanimidamide
23	2-(Dimethylamino)-N'-hydroxyethanimidamide
24	N'-Hydroxy-2-morpholin-4-ylethanimidamide
25	1-Acetyl-4-aminopiperidine hydrochloride
26	3-Methyloxetane-3-carboxylic acid
27	(4-Methylpiperazin-1-yl)acetic acid
28	(Isopropylamino)(oxo)acetic acid
29	1-Methyl-5-oxopyrrolidine-3-carboxylic acid
30	Tetrahydro-2H-pyran-4-carboxylic acid
31	Morpholin-4-ylacetic acid
32	Tert-butoxyacetic acid

33	Methyl (2*S*)-2-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-hydroxypropanoate
34	1-Ethyl-*N*-(2-hydroxy-1-methylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
35	Ethyl 4-ethoxy-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
36	Ethyl 4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
37	Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
38	Ethyl 1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
39	1-n-Propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
40	N'-Acetyl 1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
41	Ethyl 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
42	1-Ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
43	1-Ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
44	1-Ethyl-*N*-[(1*S*)-2-hydroxy-1-(phenylmethyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
45	1-Ethyl-*N*-[(1*R*)-2-hydroxy-1-(phenylmethyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
46	1-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
47	1-Ethyl-*N*-[(2*R*)-2-hydroxy-2-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
48	1-Ethyl-*N*-[(2*S*)-2-hydroxy-2-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
49	1-Ethyl-*N*-(2-hydroxy-1,1-dimethylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
50	*N*-methyltetrahydro-2*H*-pyran-4-amine
51	Ethyl 1-ethyl-4-[methyl(tetrahydro-2*H*-pyran-4-yl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
52	1-Ethyl-4-[methyl(tetrahydro-2*H*-pyran-4-yl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
53	N'-Acetyl-1-ethyl-4-[methyl(tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide
54	*trans*-4-Aminocyclohexanol
55	Tetrahydro-2*H*-pyran-3-amine hydrochloride
56	4-Aminocyclohexanone hydrochloride
57	*N*-Propyltetrahydro-2*H*-pyran-4-amine

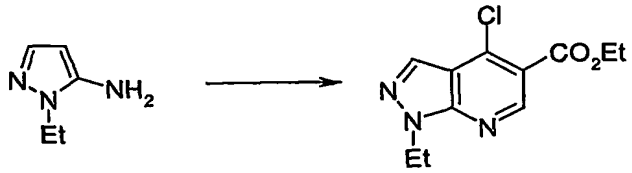
58	Ethyl 4-chloro-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
59	Ethyl 1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
60	1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
61	*N'*-(2,2-Dimethylpropanoyl)-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
62	1,1-Dimethylethyl 2-{[1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}hydrazinecarboxylate
63	1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide hydrochloride
64	1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N'*-(tetrahydro-2*H*-pyran-4-ylcarbonyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
65	*N'*-(Cyclobutylcarbonyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
66	1-Ethyl-*N'*-[(5-oxo-2-pyrrolidinyl)carbonyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide (non-preferred name)
67	*N*-[2-(2-{[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}hydrazino)-2-oxoethyl]acetamide (non-preferred name)
68	1-Ethyl-*N'*-[(1-methyl-2-piperidinyl)carbonyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
69	1-Ethyl-*N'*-[(4-methyl-1,2,5-oxadiazol-3-yl)acetyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
70	1-Ethyl-*N'*-[(3-oxocyclopentyl)carbonyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
71	1-Ethyl-*N'*-(tetrahydro-3-furanylcarbonyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
72	1-ethyl-*N'*-[(2-oxo-1,3-thiazolidin-4-yl)carbonyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
73	*N'*-[(2,2-Dimethylcyclopropyl)carbonyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
74	*N*-[2-(2-{[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}hydrazino)-2-oxoethyl]-*N*-methylacetamide (non-preferred name)
75	1-Ethyl-*N'*-(tetrahydro-2*H*-pyran-4-ylacetyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
76	1-Ethyl-*N'*-[(1-methylcyclobutyl)carbonyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
77	1-Ethyl-*N'*-[(3-methyl-5-isoxazolyl)carbonyl]-4-(tetrahydro-2*H*-pyran-

	4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
78	1-Ethyl-*N'*-[(1-methyl-1*H*-pyrazol-5-yl)carbonyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
79	*N'*-[(1-Acetyl-4-piperidinyl)carbonyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
80	(1*E/Z*)-*N*-hydroxy-2-(4-methyl-1-piperazinyl)ethanimidamide
81	4-Fluoro-*N*-hydroxybenzenecarboximidamide
82	(1*E/Z*)-*N*-hydroxy-3-oxo-3-(1-pyrrolidinyl)propanimidamide
83	{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}acetic acid
84	1,1-Dimethylethyl {5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}acetate
85	1,1-Dimethylethyl (3*E/Z*)-3-(hydroxyamino)-3-iminopropanoate
86	*N''*-{[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}-*N,N,N',N'*-tetramethylcarbonohydrazonic diamide
87	Ethyl (2-methyl-1,3-thiazol-4-yl) acetate
88	2-Methyl-1,3-thiazol-4-yl acetic acid
89	1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N'*-(1*H*-1,2,3-triazol-1-ylacetyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
90	*N'*-[(2,4-Dimethyl-1,3-thiazol-5-yl)acetyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
91	1-Ethyl-*N'*-(2-furanylacetyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
92	1-Ethyl-*N'*-(3-isoxazolylacetyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
93	1-Ethyl-*N'*-{[4-(methyloxy)phenyl]acetyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
94	1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N'*-(1*H*-tetrazol-1-ylacetyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
95	1-Ethyl-*N'*-(5-isothiazolylacetyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
96	1-Ethyl-*N'*-[(3-methyl-5-isoxazolyl)acetyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
97	*N'*-{[4-(Dimethylamino)phenyl]acetyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
98	1-Ethyl-*N'*-[(2-methyl-1,3-thiazol-4-yl)acetyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
99	2-{1-[2-(2-{[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}hydrazino)-2-oxoethyl]cyclopentyl}-*N*-methylacetamide
100	*N*-[2-(2-{[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}hydrazino)-2-

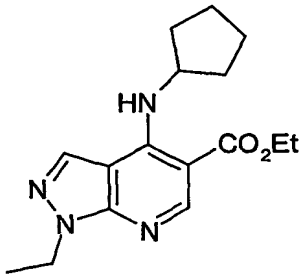
	oxoethyl]cyclopropanecarboxamide (non-preferred name)
101	1-Ethyl-*N'*-[(5-methyl-3-isoxazolyl)carbonyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
102	1-Ethyl-*N'*-[(5-methyl-3-isoxazolyl)acetyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
103	1-Ethyl-*N'*-[3-(4-methyl-1,3-thiazol-5-yl)propanoyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
104	1-Ethyl-*N'*-[(6-oxo-2-piperidinyl)carbonyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
105	1-Ethyl-*N'*-[(3-methyl-1*H*-1,2,4-triazol-5-yl)acetyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
106	*N'*-[(3,5-Dimethyl-4-isoxazolyl)acetyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
107	*N*-[2-(2-{[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}hydrazino)-1-methyl-2-oxoethyl]acetamide (non-preferred name)
108	*N'*-[(1-Acetyl-4-piperidinyl)acetyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
109	1-Ethyl-*N'*-[(4-methylphenyl)acetyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
110	1-Ethyl-*N'*-[(4-methylphenyl)carbonyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
111	*N'*-[(3,4-Dimethylphenyl)carbonyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
112	*N'*-[(2,4-Dimethylphenyl)carbonyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
113	*N'*-[(2,4-Dimethylphenyl)acetyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
114	*N'*-[(4-Bromophenyl)acetyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide
115	4-Fluoro-*N*-hydroxybenzenecarboximidamide
116	1,1-Dimethylethyl [(2*Z*)-2-(hydroxyamino)-2-iminoethyl]carbamate
117	1,1-Dimethylethyl ({5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)carbamate
118	5-[3-(Aminomethyl)-1,2,4-oxadiazol-5-yl]-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
119	4-Chloro-*N*-({5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)butanamide
120	5-Chloro-*N*-({5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)pentanamide
121	(1*E*/*Z*)-*N*-hydroxy-2-(4-morpholinyl)propanimidamide
122	(1*E*/*Z*)-2-cyclohexyl-*N*-hydroxyethanimidamide
123	1,1-Dimethylethyl 4-[(2*Z*)-2-(hydroxyamino)-2-iminoethyl]-1-

	piperidinecarboxylate
124	1,1-Dimethylethyl 4-({5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-1-piperidinecarboxylate
125	1-Ethyl-5-[3-(4-piperidinylmethyl)-1,2,4-oxadiazol-5-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine hydrochloride
126	*N*-Hydroxy-1-(phenylsulfonyl)cyclopropanecarboximidamide
127	(1*E*/*Z*)-*N*-Hydroxy-2-phenylethanimidamide
128	(*1E*/*Z*)-*N*-Hydroxy-2-phenylpropanimidamide
129	(*1E*/*Z*)-*N*-Hydroxy-2-[4-(methyloxy)phenyl]ethanimidamide
130	(*1E*/*Z*)-*N*-Hydroxy-2-[3-(methyloxy)phenyl]ethanimidamide
131	(*1E*/*Z*)-2-[4-(Dimethylamino)phenyl]-*N*-hydroxyethanimidamide
132	(*1E*/*Z*)-2-[3-(Dimethylamino)phenyl]-*N*-hydroxyethanimidamide
133	(*1E*/*Z*)-*N*-Hydroxy-2-(phenyloxy)ethanimidamide
134	(1*E*/*Z*)-*N*-hydroxy-2-(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)ethanimidamide
135	(*1E*/*Z*)-*N*-Hydroxy-2-(4-phenyl-1-piperazinyl)ethanimidamide
136	1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
137	1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile
138	1-Ethyl-*N*-hydroxy-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboximidamide
139	1-Ethyl-*N*-[4-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

Intermediate 1: Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
Prepared from commercially available 5-amino-1-ethyl pyrazole as described by G. Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027:

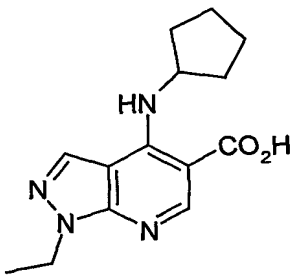


Intermediate 2: Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



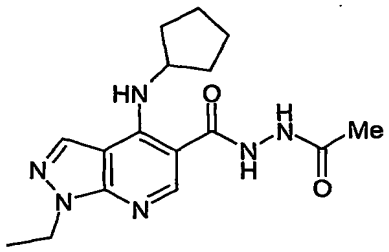
Intermediate 1 (0.051g) and cyclopentyl amine (0.019g) were suspended in ethanol (2ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 16h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM and water. The organic layer was loaded directly onto an SPE cartridge (silica, 5g) and eluted sequentially with; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O, (v) EtOAc and (vi) MeOH. Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 2 (0.074g). LCMS showed $MH^+ = 303$; T_{RET} = 3.45min

Intermediate 3: 4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



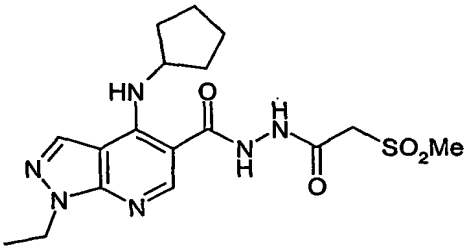
A solution of Intermediate 2 (2.2g) in ethanol: water (95:5, 16.85ml) was treated with sodium hydroxide (1.2g) and heated at 50°C for 16h. The mixture was concentrated in vacuo and the residue re-dissolved in water (0.85ml). The solution was acidified to pH4 using acetic acid and the resultant white precipitate was collected by filtration and dried under vacuum to afford Intermediate 3 (1.9g). LCMS showed $MH^+ = 275$; T_{RET} = 2.65min

Intermediate 4: N'-Acetyl-4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide



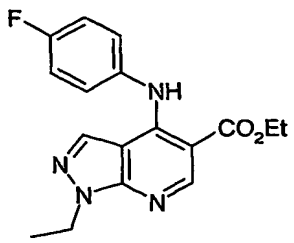
Intermediate 3 (0.066g), EDC (0.06g) and HOBT (0.035g) were suspended in DMF (2ml) and the mixture was stirred for 15 minutes. Acetic hydrazide (0.02g) was then added and the mixture stirred under nitrogen for 18h. Solvents were removed by concentration in vacuo and the residue partitioned between DCM and water. The layers were separated and the organic phase was washed with saturated aqueous sodium bicarbonate solution, then concentrated and applied to an SPE cartridge (aminopropyl, 1g) which was eluted with methanol. Concentration in vacuo afforded Intermediate 4 (0.043g). LCMS showed $MH^+ = 331$; $T_{RET} = 2.38$min.

Intermediate 5: 4-(Cyclopentylamino)-1-ethyl-N'-[(methylsulfonyl)acetyl]-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide



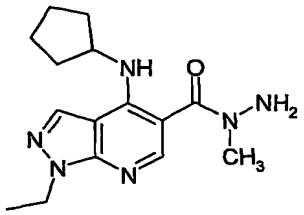
Intermediate 3 (0.12g), EDC (0.12g) and HOBT (0.072g) were suspended in DMF (2ml) and stirred for 15 minutes. Intermediate 8 (0.082g) was then added and the mixture stirred under nitrogen for 18h. Reaction was incomplete so a further portion of Intermediate 8 was added (0.040g) and stirring continued for a further 66h. Solvents were removed in vacuo and the residue partitioned between DCM and water. The aqueous phase was further extracted with DCM and the combined organic layers applied to an SPE cartridge (silica, 5g) which was eluted sequentially with a gradient of Et_2O: MeOH (1:0, 9:1, 8:2, 7:3 and 6:4). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 5 (0.154g). LCMS showed $MH^+ = 409$; $T_{RET} = 2.42$min.

Intermediate 6: Ethyl 4-(4-fluorophenylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



Intermediate 1 (0.051g) and 4-fluoroaniline (0.024g) were suspended in ethanol (2ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 16h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM and water. The organic layer was loaded directly onto an SPE cartridge (silica, 5g) and eluted sequentially with; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O, (v) EtOAc, (vi) MeOH. Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 6 (0.077g). LCMS showed $MH^+ = 328$; $T_{RET} = 3.36$min.

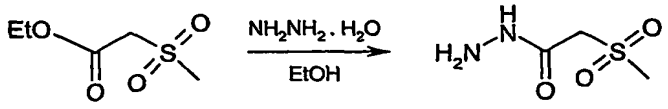
Intermediate 7: 4-(Cyclopentylamino)-1-ethyl-N-[methyl]-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide



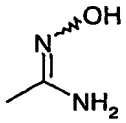
Intermediate 3 (0.10g) was dissolved in DMF (2ml) and treated with HBTU (0.136g) and DIPEA (0.116g). A separate portion of Intermediate 3 (0.10g) was dissolved in DMF (2ml) and treated with EDC (0.096g) and HOBT (0.058g). The resultant suspensions were both stirred under nitrogen for 15min, then methyl hydrazine (0.017g) added to each and stirring continued under nitrogen for 18h. The mixtures were independently concentrated in vacuo and the residues partitioned between DCM and water. The organic layers were concentrated and each applied to an SPE cartridge (aminopropyl, 2g) which was eluted with methanol, followed by 10% ammonia in methanol. The two portions of Intermediate 7 thus afforded were combined (0.16g). LCMS showed $MH^+ = 303$; $T_{RET} = 2.22$min.

Intermediate 8: Methanesulfonyl acetic acid hydrazide

Prepared from commercially available ethyl methylsulphonyl acetate as described by D. E. Bays et. al. in EP 50407 :

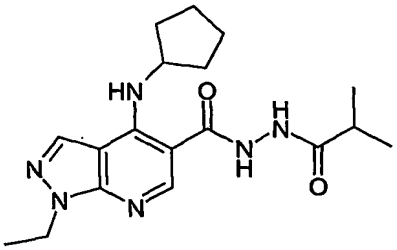


Intermediate 9: Acetamidoxime



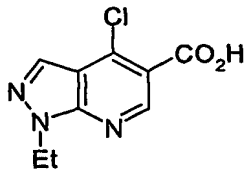
Can be prepared from aqueous hydroxylamine and acetonitrile as described by J. J. Sahbari et. al. in WO 00/032565.

Intermediate 10: 4-(Cyclopentylamino)-1-ethyl-N'-isobutyryl-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide



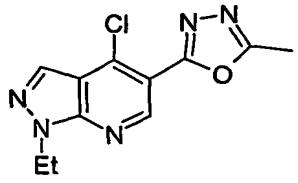
Intermediate 3 (0.060g), EDC (0.06g) and HOBT (0.035g) were suspended in DMF (2ml) and stirred under nitrogen for 15 minutes. Isobutyric acid hydrazide (0.027g) was then added and the mixture stirred under nitrogen for 18h. Solvents were removed in vacuo and the residue partitioned between DCM and water. The organic phase was washed with saturated aqueous sodium bicarbonate solution, then concentrated in vacuo and applied to an SPE cartridge (aminopropyl, 1g) which was eluted with methanol. Concentration in vacuo afforded Intermediate 10. LCMS showed $MH^+ = 359$; $T_{RET} = 2.70$min.

Intermediate 11: 4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



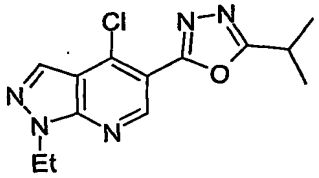
A solution of Intermediate 1 (3.5g) in dioxane (28ml) was treated with potassium hydroxide (6.3g) as a solution in water (20ml). The mixture was stirred for 2h, then concentrated in vacuo, acidified to pH 3 with 2M aqueous hydrochloric acid and extracted with ethyl acetate. The layers were separated, the organic layer dried over sodium sulphate, then concentrated in vacuo to afford Intermediate 11 as a white solid (2.4g). LCMS showed $MH^+ = 226$; $T_{RET} = 2.62$min.

Intermediate 12: 4-Chloro-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridine



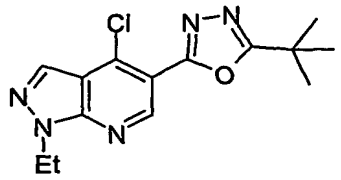
Intermediate 11 (0.4g) was dissolved in thionyl chloride (3ml) and the mixture was heated at reflux (95°C) with stirring for 1h. After cooling to room temperature, excess thionyl chloride was removed by evaporation under reduced pressure and the resultant solid dissolved in anhydrous acetonitrile (2ml). This solution was added to a solution of acetic hydrazide (0.145g) and diisopropylethylamine (0.465ml) in anhydrous acetonitrile (2ml), and the mixture stirred for a further 2h. The mixture was concentrated in vacuo and the residue treated directly with phosphorus oxychloride (4ml). The resultant solution was stirred and heated at reflux (120°C) for 0.5h, then allowed to cool and purified by Biotage (silica, 40g), eluting with cyclohexane : EtOAc (1:1) to afford Intermediate 12 (0.32g). LCMS showed $MH^+ = 264$; $T_{RET} = 2.55$ min.

Intermediate 13: 4-Chloro-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridine



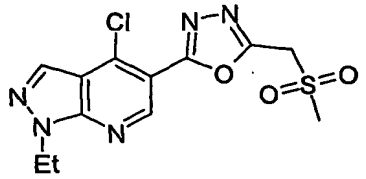
Intermediate 11 (0.05g) was dissolved in thionyl chloride (1ml) and the mixture was heated at reflux (95°C) with stirring for 1h. After cooling to room temperature, excess thionyl chloride was removed by evaporation under reduced pressure and the resultant solid dissolved in anhydrous acetonitrile (0.5ml). This solution was added to a solution of isobutyric acid hydrazide (0.025g) and diisopropylethylamine (0.058ml) in anhydrous acetonitrile (1ml), and the mixture stirred for a further 1.5h. The mixture was concentrated in vacuo and the residue treated directly with phosphorus oxychloride (2ml). The resultant solution was stirred and heated at reflux (120°C) for 2h, then allowed to cool and concentrated in vacuo. The residue was applied to an SPE cartridge (silica, 5g) which was eluted sequentially with a gradient of EtOAc : cyclohexanI (i) 1:16, (ii) 1:8, (iii) 1:4, (iv) 1:2, (v) 1:1 and (vi) 1:0. Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 13 (0.049g). LCMS showed $MH^+ = 292$; $T_{RET} = 2.96$min.

Intermediate 14: 5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine



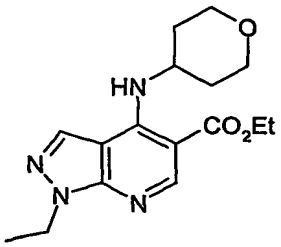
Intermediate 11 (0.40g) was dissolved in thionyl chloride (3ml) and the mixture was heated at reflux (95°C) with stirring for 1h. After cooling to room temperature, excess thionyl chloride was removed by evaporation under reduced pressure and the resultant solid dissolved in anhydrous acetonitrile (2ml). This solution was added to a solution of pivalic acid hydrazide (0.228g) and diisopropylethylamine (0.465ml) in anhydrous acetonitrile (2ml), and the mixture stirred for a further 1.5h. The mixture was concentrated in vacuo and the residue treated directly with phosphorus oxychloride (5ml). The resultant solution was stirred and heated at reflux (120°C) for 1.5h, then allowed to cool, concentrated in vacuo and purified by Biotage (silica, 40g), eluting with petroleum ether (40/60) : EtOAc (1:1) to afford Intermediate 14 (0.388g). LCMS showed MH^+ = 306; T_{RET} = 3.14 min.

Intermediate 15: 4-Chloro-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridine



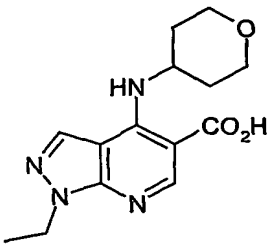
Intermediate 11 (0.68g) was dissolved in thionyl chloride (4ml) and the mixture was heated at reflux (95°C) with stirring for 1h. After cooling to room temperature, excess thionyl chloride was removed by evaporation under reduced pressure and the resultant solid dissolved in anhydrous acetonitrile (3ml). This solution was added dropwise over 5 minutes to a solution of Intermediate 8 (0.504g) and diisopropylethylamine (0.787ml) in anhydrous acetonitrile (12ml), and the mixture then stirred for a further 1h. The mixture was concentrated in vacuo and the residue treated directly with phosphorus oxychloride (8ml). The resultant solution was stirred and heated at reflux (120°C) for 2.5h, then allowed to cool, concentrated in vacuo and purified by Biotage (silica, 40g), eluting first with petroleum ether (40/60) : EtOAc (2:1), then with petroleum ether (40/60) : EtOAc (1:1). Fractions containing desired material were combined, concentrated in vacuo and the residue further purified by trituration with diethyl ether to afford Intermediate 15 (0.41g). LCMS showed MH^+ = 342; T_{RET} = 2.46 min.

Intermediate 16: Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



Intermediate 1 (0.20g) and triethylamine (0.55ml) were suspended in ethanol (8ml) and 4-aminotetrahydropyran (Intermediate 21, 0.088g) was added. The mixture was stirred under nitrogen, heated at 80°C for 16h, then concentrated in vacuo. The residue was partitioned between DCM and water. The layers were separated and the organic layer was loaded directly onto an SPE cartridge (silica, 5g) which was eluted sequentially witI; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O and (v) EtOAc. Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 16 (0.21g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.93$min.

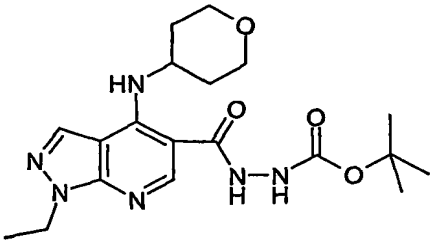
Intermediate 17: 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 16 (0.21g) in ethanol : water (95:5, 10ml) was treated with sodium hydroxide (0.12g). The mixture was heated at 50°C for 8h, then concentrated in vacuo, dissolved in water and acidified to pH 4 with acetic acid. The resultant white solid was removed by filtration and dried under vacuum to afford Intermediate 17 as an off-white solid (0.16g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.11$min.

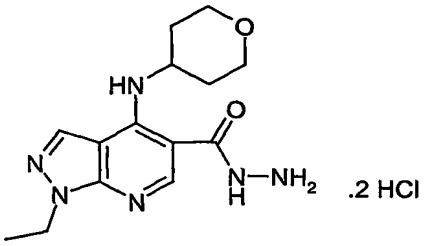
An alternative preparation of Intermediate 17 is as follows:
A solution of Intermediate 16 (37.8g) in ethanol : water (4:1, 375ml) was treated with sodium hydroxide (18.9g). The mixture was heated at 50 °C for 5 hours, then concentrated in vacuo, dissolved in water and acidified to pH 2 with aqueous hydrochloric acid (2M). The resultant white solid was removed by filtration and dried under vacuum to afford Intermediate 17 as an off-white solid (29.65g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.17$ min.

Intermediate 18: Tert-butyl 2-{[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]carbonyl}hydrazinecarboxylate



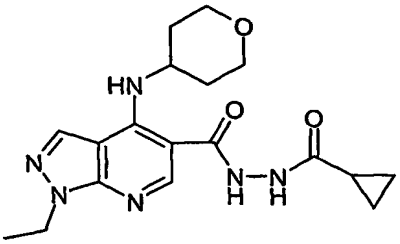
A suspension of Intermediate 17 (1.48g), EDC (1.34g) and HOBT (0.83g) in DMF (20ml) was stirred at room temperature for 30min. t-Butyl carbazate (0.68g) was then added and stirring continued under nitrogen for a further 66h. The mixture was concentrated in vacuo and the residue divided into two portions for purification. Each portion was applied to an SPE cartridge (aminopropyl, 10g) which was eluted with methanol and the combined eluents were concentrated in vacuo. Further purification was carried out by Biotage (silica, 40g), eluting with cyclohexane : ethyl acetate (1:4). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 18 (1.39g). LCMS showed $MH^+ = 405$; $T_{RET} = 2.64$min.

Intermediate 19: 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide dihydrochloride



Intermediate 18 (1.39g) was treated with a 4M solution of hydrochloric acid in dioxane (8ml) and the mixture stirred under nitrogen for 1h. Concentration in vacuo afforded Intermediate 19 as a white solid (1.17g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.04$min.

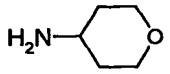
Intermediate 20: N'-(Cyclopropylcarbonyl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide



A solution of Intermediate 19 (0.045g) in THF (2ml) was treated with DIPEA (0.045ml), then with cyclopropylcarbonyl chloride (0.013g) and stirred at room temperature for 16h. The mixture was concentrated in vacuo and the residue partitioned between

dichloromethane and water. The layers were separated and the organic layer concentrated in vacuo, then applied to an SPE cartridge (aminopropyl, 1g). The column was eluted with methanol to afford Intermediate 20 as a white solid (0.02g). LCMS showed MH^+ = 373; T_{RET} = 2.15min.

Intermediate 21: 4-Aminotetrahydropyran



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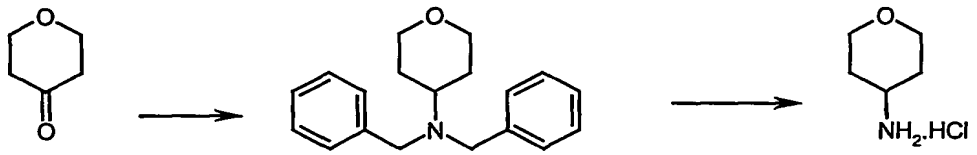
Intermediate 21A: Tetrahydro-2H-pyran-4-amine hydrochloride = 4-Aminotetrahydropyran hydrochloride



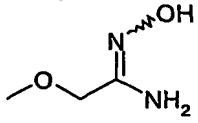
Step1: N,N-dibenzyltetrahydro-2H-pyran-4-amine

Dibenzylamine (34.5g) and acetic acid (6.7ml) were added to a stirred solution of tetrahydro-4H-pyran-4-one (16.4g, commercially available from e.g. Aldrich) in dichloromethane (260ml) at 0 °C to 5 °C. After 2.5h at 0 °C to 5 °C, sodium triacetoxyborohydride (38.9g) was added portionwise, and the mixture was allowed to warm to room temperature. After stirring at room temperature overnight, the reaction mixture was washed successively with 2M-sodium hydroxide (200ml and 50ml), water (2 x 50ml) and brine (50ml), then dried and evaporated to give a yellow oil (45g). This oil was stirred with methanol (50ml) at 4 °C for 30min to give the product as a white solid (21.5g). LCMS showed MH^+ = 282; T_{RET} = 1.98 min.

Step 2: Tetrahydro-2H-pyran-4-amine hydrochloride

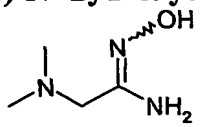
N,N-dibenzyltetrahydro-2*H*-pyran-4-amine (20.5g) was dissolved in ethanol (210ml) and hydrogenated over 10% palladium on carbon catalyst (4g) at 100 psi for 72h at room temperature. The reaction mixture was filtered and the filtrate was adjusted to pH 1 with 2M-hydrogen chloride in diethyl ether. Evaporation of solvents gave a solid which was triturated with diethyl ether to give the product as a white solid (9.23g). ^{1}H NMR (400MHz, d_6-DMSO, δppm) 8.24 (br. s, 3H), 3.86 (dd, 12, 4Hz, 2H), 3.31 (dt, 2, 12Hz, 2H), 3.20 (m, 1H), 1.84 (m, 2H), 1.55 (dq, 4, 12Hz, 2H).

Intermediate 22: N'-Hydroxy-2-methoxyethanimidamide



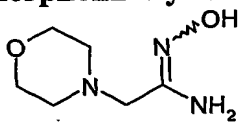
A solution of methoxyacetonitrile (12.26g) in ethanol (220ml) was treated with hydroxylamine hydrochloride (11.95g) followed by potassium carbonate (22.9g) and heated under reflux for 2 days. The mixture was concentrated in vacuo, then partitioned between ethylacetate and water. The organic layer was concentrated in vacuo to afford Intermediate 22 as a colourless liquid (7.6g). ^{1}H NMR ($CDCl_3$) 7.16 (3H, s), 7.67 (s, 2H), 9.32 (brs, 2H), 13.08 (1H, s).

Intermediate 23: 2-(Dimethylamino)-N'-hydroxyethanimidamide



Can be prepared in an analogous manner to Intermediate 9, starting from dimethylamino acetonitrile.

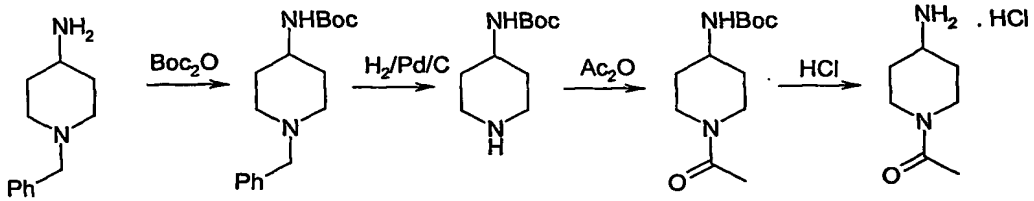
Intermediate 24: N'-Hydroxy-2-morpholin-4-ylethanimidamide



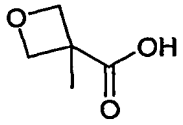
Can be prepared in an analogous manner to Intermediate 9, starting from morpholino acetonitrile (itself commercially available from TCI America, 9211 North Harborgate Street, Portland, OR 97203, USA).

Intermediate 25: 1-Acetyl-4-aminopiperidine hydrochloride

Prepared from commercially available N1-benzyl-4-aminopiperidine as described by Yamada *et. al.* In WO 00/42011:

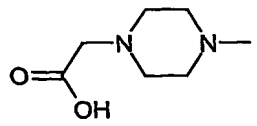


Intermediate 26: 3-Methyloxetane-3-carboxylic acid



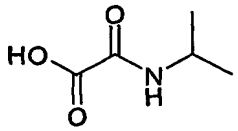
Can be prepared by oxidation of 3-Methyl-3-oxetanemethanol (commercially available from e.g. Fluka, CAS (Chemical Abstracts) Registry Number 3143-02-0) according to the procedure described by H. Fiege *et. al.* in DE3618142.

Intermediate 27: (4-Methylpiperazin-1-yl)acetic acid



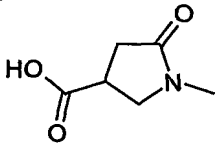
Commercially available from ChemPacific USA Sales Marketing and Research Center, 6200 Freeport Centre, Baltimore, MD 21224, USA (CAS Registry Number 54699-92-2).

Intermediate 28: (Isopropylamino)(oxo)acetic acid



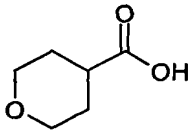
Commercially available from Austin Chemical Company, Inc., 1565 Barclay Blvd., Buffalo Grove, IL 60089, USA. CAS (Chemical Abstracts) Registry Number 3338-22-5.

Intermediate 29: 1-Methyl-5-oxopyrrolidine-3-carboxylic acid



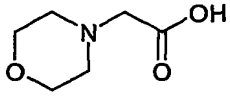
Commercially available from MicroChemistry-RadaPharma, Shosse Entusiastov 56, Moscow 111123, Russia. CAS (Chemical Abstracts) Registry Number 42346-68-9.

Intermediate 30: Tetrahydro-2H-pyran-4-carboxylic acid



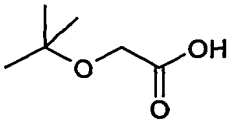
Commercially available from Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126, USA. CAS (Chemical Abstracts) Registry Number 5337-03-1.

Intermediate 31: Morpholin-4-ylacetic acid



Can be prepared from ethyl bromoacetate as described by Z. Dega-Szafran et. al. in *J. Molecular Structure*, 2001, 560, 261-273.

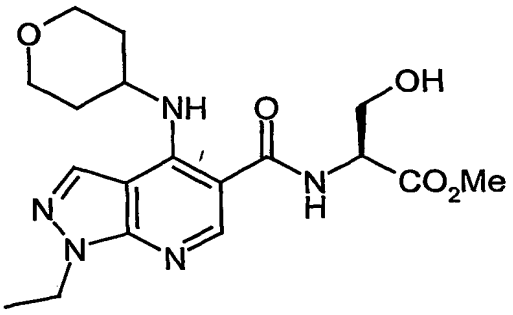
Intermediate 32: Tert-butoxyacetic acid



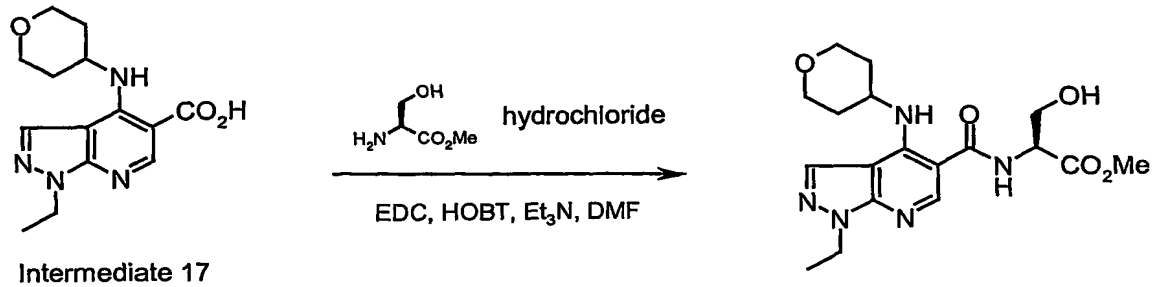
A suspension of sodium t-butoxide (24.1g) in t-butanol (150ml) was cooled in a water bath and treated drop-wise with a solution of chloroacetic acid (11.4g) in t-butanol

(30ml). The mixture was heated under reflux for 5h then concentrated in vacuo. The resultant white solid was dried in vacuo for 16h then water (100ml) was added and the mixture was filtered. The filtrate was treated with diethyl ether (150ml), then cooled in an ice bath, stirred and acidified to pH1 with 2N sulphuric acid. The layers were separated and the aqueous layer was further extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford Intermediate 32 (11.1g). ^1H NMR (400MHz; $CDCl_3$, δppm) 1.27 (9H, s), 4.04 (2H, s).

Intermediate 33: Methyl (2*S*)-2-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-hydroxypropanoate



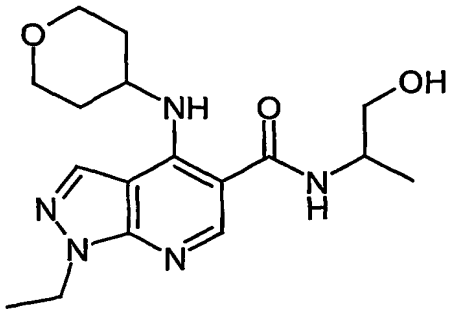
Reaction scheme:



Intermediate 17

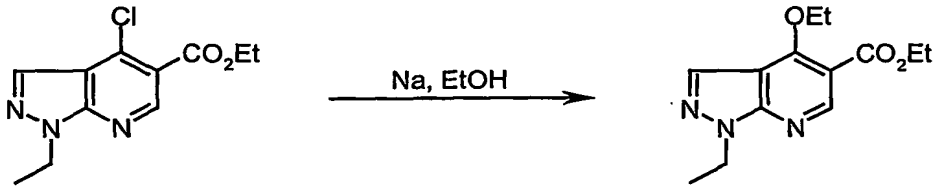
Intermediate 17 (0.1g, 0.34mmol), EDC (0.066g, 0.34mmol) and HOBT (0.05g, 0.37mmol) were suspended in DMF (2ml) and stirred at room temperature under nitrogen for 15 mins. L-Serine methyl ester hydrochloride (0.054g, 0.34mmol) and triethylamine (0.036g, 0.36mmol) were added and the mixture stirred at room temperature under nitrogen for 18 hours. Solvents were removed in vacuo and the residue was partitioned between DCM and water. The organic layer was concentrated in vacuo and applied to an SPE cartridge (aminopropyl, 5g), which was eluted with methanol. Concentration in vacuo afforded an impure residue which was further purified by SPE cartridge (silica, 5g), eluting with ethyl acetate followed by 5% methanol/ethyl acetate. The desired fractions were concentrated in vacuo to afford Intermediate 33 (0.055g). LCMS showed $MH^+ = 393$; $T_{RET} = 2.22$min.

Intermediate 34: 1-Ethyl-*N*-(2-hydroxy-1-methylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide



Intermediate 17 (0.1g, 0.34mmol), EDC (0.066g, 0.34mmol) and HOBT (0.05g, 0.37mmol) were suspended in DMF (2ml) and stirred at room temperature under nitrogen for 15 min. 2-aminopropan-1-ol (0.026g, 0.34mmol) and triethylamine (0.036g, 0.36mmol) were added and the mixture was stirred at room temperature under nitrogen for 6 hours. Solvents were removed in vacuo and the residue partitioned between DCM and water. The organic layer was concentrated and applied to an SPE cartridge (aminopropyl, 5g), which was eluted with methanol. Concentration in vacuo afforded Intermediate 34 (0.095g). LCMS showed $MH^+ = 348$, $T_{RET} = 2.15$min.

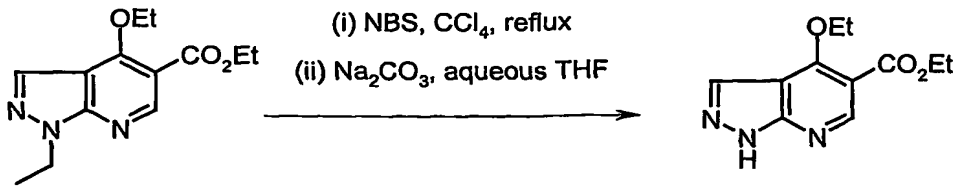
Intermediate 35: Ethyl 4-ethoxy-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



Intermediate 1 Intermediate 35

Sodium (0.55g, 23.7mmol) was added portionwise to anhydrous ethanol (25ml) at 20 °C under an atmosphere of nitrogen. After stirring for 1 hour the solution was added to Intermediate 1 (4.622g, 18.22mmol) and the reaction mixture heated at reflux for 2 hours. The mixture was evaporated in vacuo and the residue partitioned between dichloromethane and water. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated in vacuo. The residue was purified on SPE cartridges (silica, 4 x 20g) eluting with dichloromethane, ethyl acetate:petroleum ether (1:4, 1:2 then 1:1) followed by ethyl acetate). Appropriate fractions were combined and evaporated in vacuo to afford Intermediate 35 as white solid (4.33g). LCMS showed $MH^+ = 264$, $T_{RET} = 2.77$min.

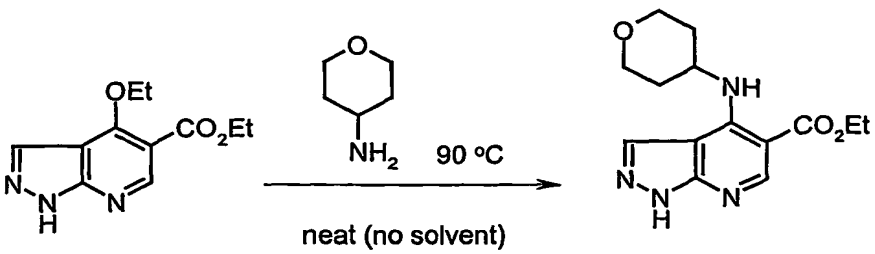
Intermediate 36: Ethyl 4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



Intermediate 35 Intermediate 36

A mixture of Intermediate 35 (1.0g, 3.8mmol) and N-bromosuccinimide (1.49g, 8.4mmol) in carbon tetrachloride (35ml) was heated at reflux for 3 hours. The reaction mixture was cooled in an ice-bath and the precipitate filtered. The filtrate was concentrated in vacuo and the residue dissolved in tetrahydrofuran (12.5ml). Water (3.5ml) and saturated sodium carbonate solution (3ml) were added and the mixture stirred at 20 °C for 18 hours. The reaction was diluted with water and extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified on an SPE cartridge (silica, 20g) eluting with dichloromethane, chloroform, then chloroform:methanol (99:1, 49:1, 19:1 then 9:1). Appropriate fractions were combined and evaporated in vacuo to afford Intermediate 36 as an off-white solid (0.45g). LCMS showed $MH^+ = 236$, $T_{RET} = 2.46$min.

Intermediate 37: Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

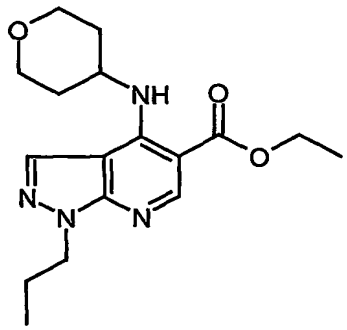


Intermediate 36 Intermediate 37

Method 1: Intermediate 36 (0.035g) was placed in a Reactivial™ and treated with 4-aminotetrahydropyran (0.05ml). The mixture was heated at 90 °C for 1.5 hours, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated. The crude product was purified by mass directed autoprep HPLC to afford Intermediate 37 as an off-white solid (0.011g). LCMS showed MH^+= 291; T_{RET} = 2.08 min.

Alternative Method 2: Intermediate 36 (2g) was suspended in 4-aminotetrahydropyran (2g), and the mixture was heated at 90 °C for 6 hours. The residual mixture was allowed to cool to room temperature and partitioned between chloroform (50ml) and water (50ml). The phases were separated and the organic phase was evaporated to dryness. The residue was triturated with Et_2O (30ml) and the insoluble solid was collected and dried to afford Intermediate 37 as a cream solid (2.24g). LCMS showed MH^+= 291; T_{RET} = 2.19 min.

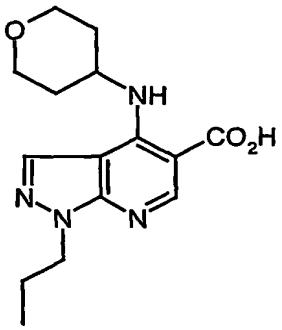
Intermediate 38: Ethyl 1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



Sodium hydride (0.067 g, 60% dispersion in oil) was added to a stirred solution of Intermediate 37 (0.47 g) in DMF (19 ml), followed by n-propyl iodide (0.17 ml). The mixture was stirred at 23 °C for 16 hours, then concentrated, diluted with chloroform (30 ml) and washed with 1:1 water:brine solution (30 ml), separated and the organic layer concentrated. The residue was purified on a SPE cartridge (silica, 10 g) eluting with 10 ml volumes of dichloromethane, 1:1 diethyl ether:cyclohexane, and diethyl ether. The combined 1:1 diethyl ether: cyclohexane, and diethyl ether, fractions were concentrated

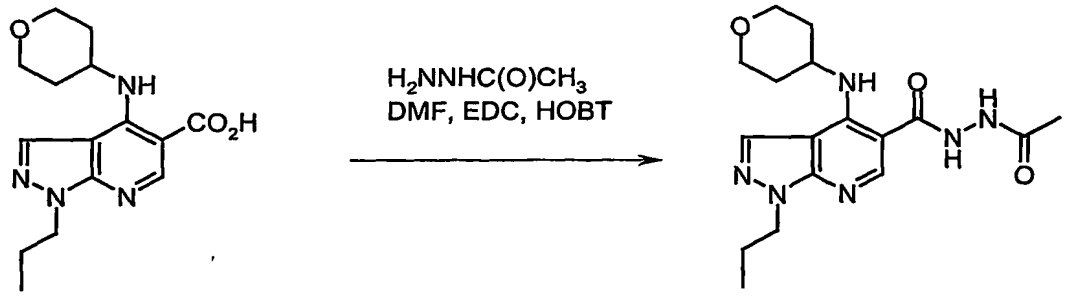
to give Intermediate 38 as a clear gum (0.23 g). LCMS showed $MH^+ = 333$; $T_{RET} = 3.14$ min.

Intermediate 39: 1-n-Propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



2M-Sodium hydroxide solution (0.7 ml) was added to a stirred suspension of Intermediate 38 (0.23 g) in ethanol (5 ml) and water (1.5 ml). After stirring overnight at room temperature, a further quantity of 2M-sodium hydroxide solution (0.7 ml) was added, and the reaction mixture was heated at 43 °C for 2.5 hours. The reaction solution was concentrated, diluted with water (5 ml) and acidified with 2M-hydrochloric acid. The resulting precipitate was collected by filtration, washed with water and dried to give Intermediate 39 as a white solid (0.14 g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.42$min.

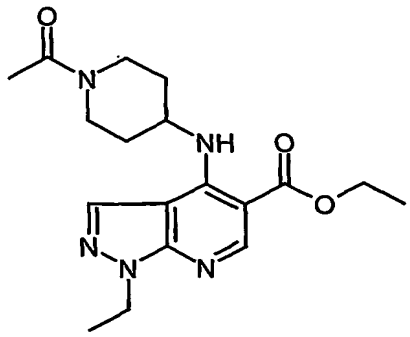
Intermediate 40: N'-Acetyl 1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide



Intermediate 39 Intermediate 40

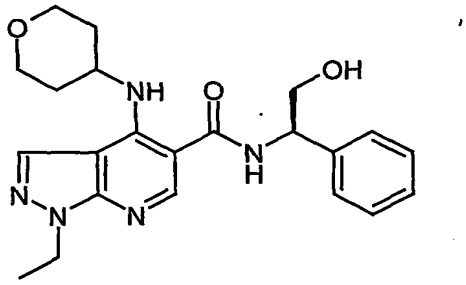
Intermediate 40 can be made from Intermediate 39 in a similar way to the process described for Intermediate 4, for example using a similar or the same number of moles of reagents and/or volumes of solvents.

Intermediate 41: Ethyl 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



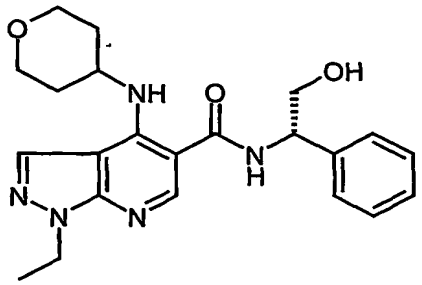
Intermediate 1 (0.079g, 0.56mmol), Intermediate 25 (0.129g, 0.51mmol) and diisopropylethylamine (0.45ml, 2.55mmol) in acetonitrile (2ml) were heated at 85 °C for 36 hours. The reaction mixture was concentrated in vacuo and the residue partitioned between DCM and water. The phases were separated using a hydrophobic frit (Whatman). The organic phase was evaporated in vacuo and the residue applied to an SPE cartridge (silica, 5g). The cartridge was eluted with EtOAc and then DCM / MeOH (1:1). Fractions containing the desired material were combined and concentrated in vacuo to afford Intermediate 41 (0.1g). LCMS showed $MH^+ = 360$; $T_{RET} = 2.63$min.

Intermediate 42: 1-Ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide



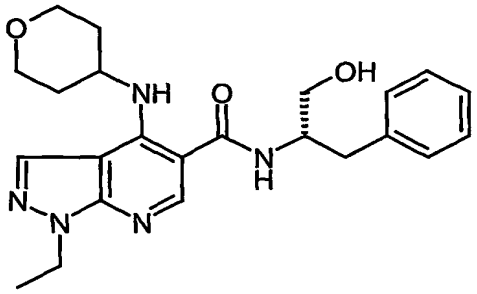
Intermediate 17 (0.25g, 0.86mmol), EDC (0.23g, 1.2mmol) and HOBT (0.139g, 1.03mmol) were suspended in DMF (5ml) and the suspension was stirred at room temperature. After 25min, (2*R*)-2-Amino-2-phenylethanol (0.13g, 0.95mmol, commercially available from Aldrich) was added, and the mixture was stirred at room temperature for 20 hours. Solvents were removed in vacuo and the residue was dissolved in DCM (50ml) and washed successively with water (25ml) and 5% sodium hydrogen carbonate solution (25ml). The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was dissolved in dichloromethane (5ml) and applied to a SPE cartridge (silica, 10g), which was eluted with a gradient of ethyl acetate – petroleum ether (1:2, 1:1 and 1:0). Fractions containing the desired material were combined and concentrated in vacuo to afford Intermediate 42 as a white foam (0.318g). LCMS showed $MH^+ = 410$; $T_{RET} = 2.55$min.

Intermediate 43: 1-Ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide



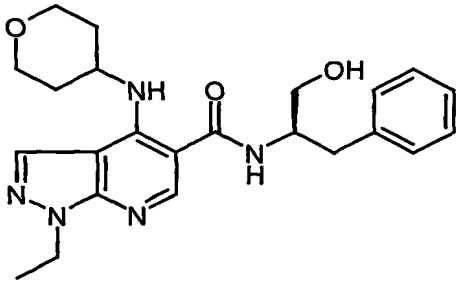
Intermediate 43 was prepared from Intermediate 17 and (2*S*)-2-amino-2-phenylethanol (commecially available from Lancaster Synthesis) using an analogous method to that for Intermediate 42. LCMS showed $MH^+ = 410$; $T_{RET} = 2.55$min.

Intermediate 44 1-Ethyl-*N*-[(1*S*)-2-hydroxy-1-(phenylmethyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide



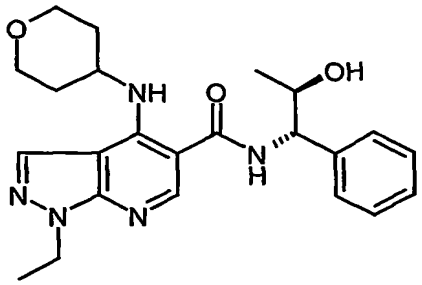
Intermediate 44 was prepared from Intermediate 17 and (2*S*)-2-amino-3-phenyl-1-propanol (commercially available from Aldrich) using an analogous method to that for Intermediate 42. LCMS showed $MH^+ = 424$; $T_{RET} = 2.60$min.

Intermediate 45: 1-Ethyl-*N*-[(1*R*)-2-hydroxy-1-(phenylmethyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide



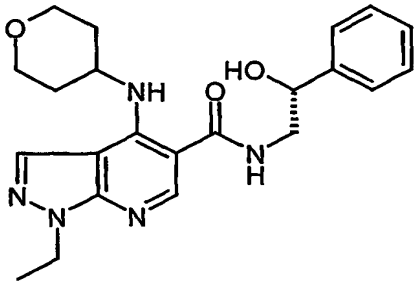
Intermediate 45 was prepared from Intermediate 17 and (2*R*)-2-amino-3-phenyl-1-propanol (commecially available from Aldrich) using an analagous method to that for Intermediate 42. LCMS showed $MH^+ = 424$; $T_{RET} = 2.59$min.

Intermediate 46: **1-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



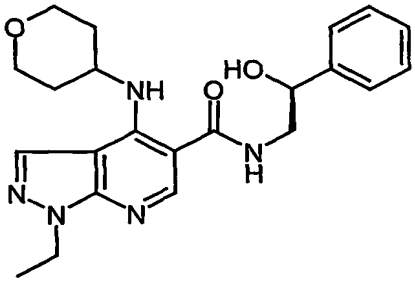
Intermediate 46 was prepared from Intermediate 17 and (1*S*,2*R*)-1-amino-1-phenyl-2-propanol hydrochloride (commercially available from Arch Corporation, 100 Jersey Avenue, Building D, New Brunswick, NJ 08901, USA) using an analogous method to that for Intermediate 42. LCMS showed $MH^+ = 424$; $T_{RET} = 2.58$min.

Intermediate 47: **1-Ethyl-*N*-[(2*R*)-2-hydroxy-2-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



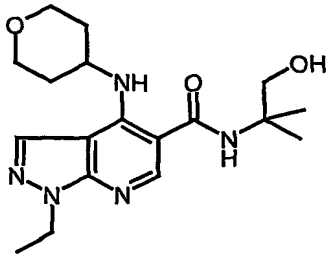
Intermediate 47 was prepared from Intermediate 17 and (1*R*)-2-amino-1-phenylethanol (commercially available from Aldrich) using an analogous method to that for Intermediate 42. LCMS showed $MH^+ = 410$; $T_{RET} = 2.62$min.

Intermediate 48: **1-Ethyl-*N*-[(2*S*)-2-hydroxy-2-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



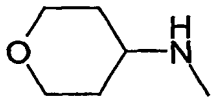
Intermediate 48 was prepared from Intermediate 17 and (1S)-2-amino-1-phenylethanol (commercially available from Fluka) using an analogous method to that for Intermediate 42. LCMS showed $MH^+ = 410$; $T_{RET} = 2.62$min.

Intermediate 49: **1-Ethyl-*N*-(2-hydroxy-1,1-dimethylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



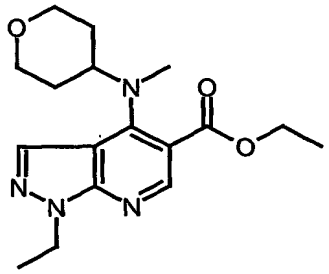
Intermediate 49 was prepared from Intermediate 17 and 2-amino-2-methyl-1-propanol (commercially available from Aldrich) using an analogous method to that for Intermediate 42. LCMS showed $MH^+ = 362$; $T_{RET} = 2.28$min.

Intermediate 50: ***N*-methyltetrahydro-2*H*-pyran-4-amine**



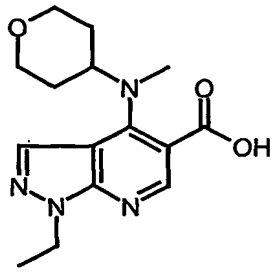
Can be prepared from tetrahydro-4H-pyran-4-one (commercially available from e.g. Sigma Aldich; CAS (Chemical Abstracts) Registry Number 29943-42-8) according to the procedure described by H.Hashimoto *et al.* in *Organic Process Research and Development* 2002, 6, 70.

Intermediate 51: **Ethyl 1-ethyl-4-[methyl(tetrahydro-2*H*-pyran-4-yl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate**



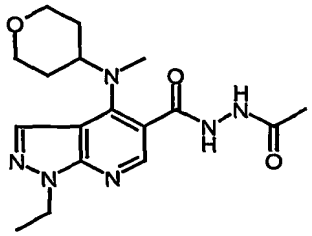
Intermediate 1 (1.2g, 4.76mmol) , Intermediate 50 (0.79g, 5.2mmol) and diisopropylethylamine (4ml, 24mmol) in MeCN (8ml) was heated at 70 °C for 24 hours. The solvent was removed in vacuo and the residue partitioned between DCM and water. The organic phase was concentrated in vacuo and the residue chromatographed on silica (50g) eluting with cyclohexane:ethyl acetate (2:1 followed by 1:1 then 1:2). Appropriate fractions were combined and evaporated to give Intermediate 51 as a brown oil (1.21g). LCMS showed $MH^+ = 334$; $T_{RET} = 2.61$min.

Intermediate 52: 1-Ethyl-4-[methyl(tetrahydro-2*H*-pyran-4-yl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



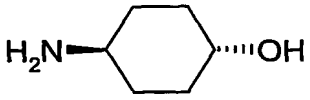
Sodium hydroxide (0.43g, 10.8mmol) was added to a solution of Intermediate 51 in ethanol (10ml, 95%). The reaction mixture was heated at 50 °C for 18 hours. The solvent was evaporated in vacuo and the residue dissolved in water and acidified to pH 3 by the addition of aqueous hydrochloric acid. The solution was extracted with DCM. The organic phase was separated using a hydrophobic frit (Whatman PTFE Folter Media with Polypropylene Housing 5μM pore size) and the solvent evaporated in vacuo to give Intermediate 52 as a white solid (0.65g). LCMS showed $MH^+ = 305$; $T_{RET} = 1.97$min.

Intermediate 53: N'-Acetyl-1-ethyl-4-[methyl(tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide



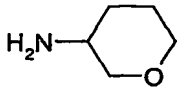
Intermediate 53 was prepared from Intermediate 52 using an analogous method to that for Intermediate 4. LCMS showed $MH^+ = 361$; $T_{RET} = 1.91$min.

Intermediate 54: ***trans*-4-Aminocyclohexanol**



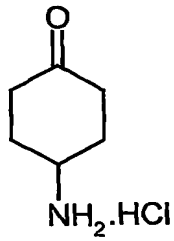
Commercially available from e.g. Acros. CAS (Chemical Abstracts) Registry Number 27489-62-9.

Intermediate 55: Tetrahydro-2*H*-pyran-3-amine hydrochloride



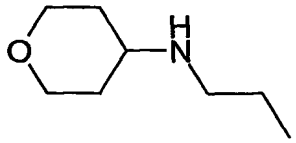
Prepared as described in *Anales De Quimica*, 1988, **84**, 148.

Intermediate 56: 4-Aminocyclohexanone hydrochloride



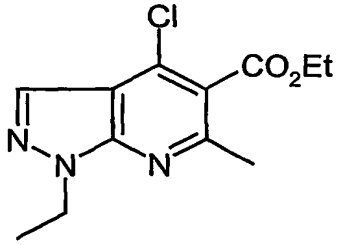
A solution of hydrogen chloride in dioxan (0.5ml, 2.0mmol, 4M) was added to a stirred solution of *tert*-butyl 4-oxocyclohexylcarbamate (0.043g, 0.20mmol, commercially available from Astatech Inc., Philadelphia, USA) in dioxan (0.5ml) and the mixture was stirred at room temperature. After 1h, the reaction mixture was evaporated to give Intermediate 56 as a cream solid (34mg). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) 8.09 (br. s, 3H), 3.51 (tt, 11, 3.5Hz, 1H), 2.45 (m, 2H, partially obscured), 2.29 (m, 2H), 2.16 (m, 2H), 1.76 (m, 2H).

Intermediate 57: *N*-Propyltetrahydro-2*H*-pyran-4-amine



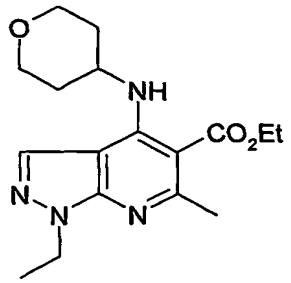
Can be prepared from tetrahydro-4H-pyran-4-one (commercially available from e.g. Sigma Aldich CAS 29943-42-8) as described by C. Zagar in WO 99/07702.

Intermediate 58: Ethyl 4-chloro-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



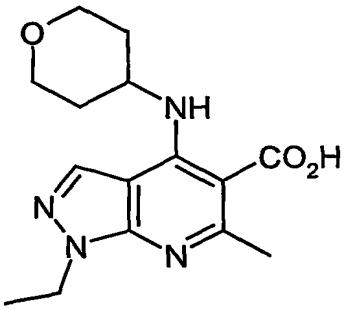
A mixture of 5-amino-1-ethylpyrazole (1.614g, 14.5mmol) and diethyl 2-(1-ethoxyethylidene)malonate (3.68g, 16.0mmol, as described by P.P.T. Sah, *J. Amer. Chem. Soc.*, 1931, 53, 1836) was heated at 150 °C under Dean Stark conditions for 5 hours. Phosphorous oxychloride (25ml) was carefully added to the mixture and the resulting solution was heated at 130 °C under reflux for 18 hours. The mixture was concentrated *in vacuo*, then the residual oil was carefully added, with cooling, to water (100ml). The resulting mixture was extracted with DCM (3x100ml) and the combined organic extracts were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residual oil was purified by Biotage chromatography (silica, 90g) eluting with ethyl acetate-petrol (1:19). Fractions containing the desired product were combined and concentrated in vacuo to afford Intermediate 58 (1.15g). LCMS showed $MH^+ = 268$; $T_{RET} = 3.18$min.

Intermediate 59: Ethyl 1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



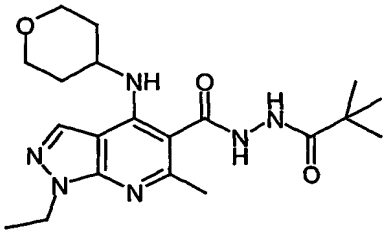
4-Aminotetrahydropyran hydrochloride (Intermediate 21, 0.413g, 3.0mmol) was added to a mixture of Intermediate 58 (0.268g, 1.0mmol) and N,N-diisopropylethylamine (0.87ml, 5.0mmol) in acetonitrile (3ml). The resulting mixture was heated at 85 °C for 24 hours. Volatiles were removed *in vacuo* and the residue was dissolved in chloroform (1.5ml) and applied to a SPE cartridge (silica, 5g). The cartridge was eluted successively with Et_2O, EtOAc and EtOAc-MeOH (9/1). Fractions containing the desired product were combined and concentrated *in vacuo* to give the desired product contaminated with starting material (Intermediate 51). Further purification using a SPE cartridge (silica, 5g) eluting with ethyl acetate-cyclohexane (1:3) afforded Intermediate 59 (0.248g). LCMS showed $MH^+ = 333$; $T_{RET} = 2.75$min.

Intermediate 60: 1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



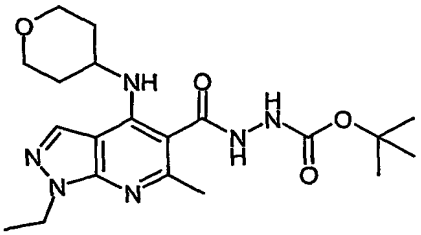
2M-Sodium hydroxide solution (0.75ml, 1.5mmol) was added to Intermediate 59 (0.248g, 0.75mmol) in ethanol (2ml), and the mixture was heated at reflux for 16 hours. The reaction mixture was concentrated, diluted with water (1ml) and acidified with 2M-hydrochloric acid (0.75ml) to precipitate a solid which was collected by filtration to afford Intermediate 60 (0.168g). LCMS showed $MH^+ = 305$; $T_{RET} = 1.86$min.

Intermediate 61: *N'*-(2,2-Dimethylpropanoyl)-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide



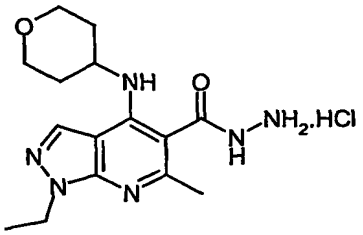
Intermediate 60 (0.255g, 0.84mmol), EDC (0.225g, 1.17mmol) and HOBT (0.136g, 1.0mmol) in DMF (5ml) was stirred at 20 °C for 75 minutes. Pivalic acid hydrazide (0.107g, 0.92mmol) was added and stirring continued for 18 hours. The reaction mixture was concentrated in vacuo and the residue partitioned between DCM and water. The organic phase was washed with aqueous sodium hydrogen carbonate then evaporated in vacuo to afford Intermediate 61 as a white solid (0.27g).). LCMS showed $MH^+ = 403$; $T_{RET} = 2.13$min.

Intermediate 62: 1,1-Dimethylethyl 2-{[1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}hydrazinecarboxylate



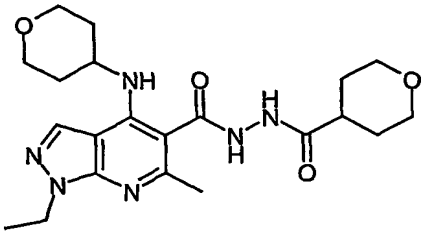
Intermediate 60 (0.253g, 0.83mmol), EDC (0.223g, 1.17mmol) and HOBT (0.135g, 1.0mmol) in DMF (5ml) was stirred at 20 °C for 30 minutes. t-Butyl carbazate (0.110g, 0.83mmol) was added and stirring continued for 18 hours. The reaction mixture was concentrated in vacuo and the residue dissolved in DMF (5ml) additional EDC (0.159g0) and HOBT (0.112g) added. After 30 minutes t-butyl carbazate (0.019g) was added and stirring continued for 18 hours. The reaction was concentrated in vacuo and the residue partitioned between DCM and water. The organic phase was washed with aqueous sodium hydrogen carbonate then evaporated in vacuo. The material was applied to a SPE cartridge (silica, 10g) and eluted with cyclohexane: ethyl acetate (1:1 followed by 2:1) to afford Intermediate 62 as a white solid (0.19g). LCMS showed $MH^+ = 419$; $T_{RET} = 2.35$min.

Intermediate 63: 1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide hydrochloride



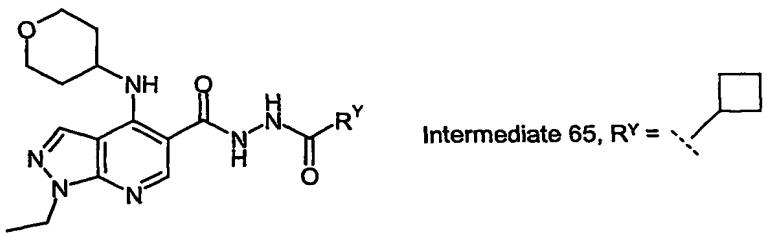
Intermediate 62 (0.19g, 0.46mmol) was dissolved in 4M hydrogen chloride in dioxane (5ml) and the reaction mixture stirred overnight at 20 °C. Concentration in vacuo afforded Intermediate 63 as a white solid (0.161g). LCMS showed $MH^+ = 319$; $T_{RET} =$ 1.72min.

Intermediate 64: 1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*'-(tetrahydro-2*H*-pyran-4-ylcarbonyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide



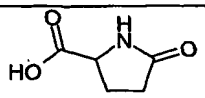
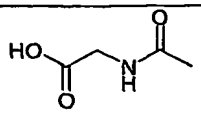
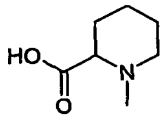
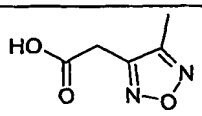
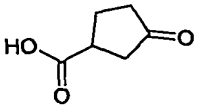
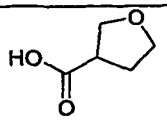
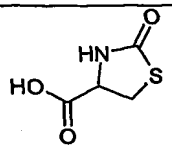
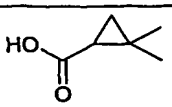
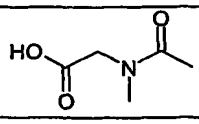
Intermediate 30 (0.06g, 0.45mmol) and TBTU (0.146g, 0.45mmol) in DMF (5ml) was stirred at 20 °C for 30 minutes. A mixture of Intermediate 63 (0.16g, 0.45mmol) and diisopropylethylamine (0.32ml, 1.82mmol) in DMF (1ml) was added and the reaction mixture stirred overnight under nitrogen. The reaction was concentrated in vacuo and the residue partitioned between DCM and water. The phases were separated using a hydrophobic frit (Whatman PTFE Folter Media with Polypropylene Housing 5μM pore size) and the organic phase evaporated in vacuo. The residue was applied to an SPE cartridge (aminopropyl, 10g) and eluted with MeOH. Appropriate fractions were concentrated in vacuo then applied to an additional SPE cartridge (silica, 2g) which was eluted sequentially with a gradient of MeOH in DCM (i) 2%, (ii) 4%, (iii) 6% and (iv) 10%. Fractions containing the desired material were combined and concentrated in vacuo to afford Intermediate 64 as a white solid (0.048g). LCMS showed $MH^+ = 431$; $T_{RET} =$ 1.87min.

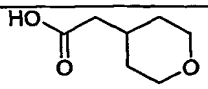
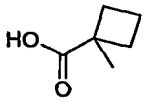
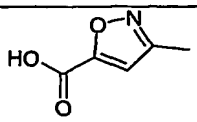
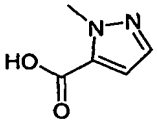
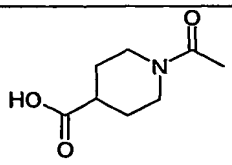
Intermediate 65: *N*'-(Cyclobutylcarbonyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide



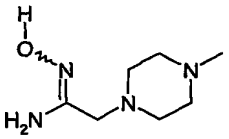
TBTU (0.050g, 0.15mmol) and diisopropylethylamine (0.04ml, 0.26 mmol) in DMF (0.5ml) was added to cyclobutylcarboxylic acid (R^YCOOH, 0.015g, 0.15mmol). The reaction mixture was stirred for 40 minutes at 20 °C. A mixture of Intermediate 19 (0.045g, 0.13mmol) and diisopropylethylamine (0.04ml, 0.26mmol) in DMF (0.5ml) was added and the reaction mixture stirred for 18h. The solvent was removed in vacuo and the residue applied to a SPE cartridge (aminopropyl, 2g). The cartridge was eluted with methanol to afford Intermediate 65 (0.052g). LCMS showed MH^+ = 387; T_{RET} = 2.28min.

Similarly prepared using the same or similar numbers of moles of reagents and/or volumes of solvents were the following:

	R^YCOOH	Source of Acid	MH^+	T_{RET} (min)
Intermediate 66		Sigma-Aldrich	416	2.03
Intermediate 67		Sigma-Aldrich	404	2.01
Intermediate 68		HCl Salt: Maybridge, or DE10008089	430	1.89
Intermediate 69		Interchim Intermediates	429	2.35
Intermediate 70		Sigma-Aldrich, or *J.Org. Chem.*, 1997, 62, 5144	415	2.12
Intermediate 71		Sigma-Aldrich	403	2.11
Intermediate 72		Sigma-Aldrich	434	2.15
Intermediate 73		ChemPacific	401	2.46
Intermediate 74		Sigma-Aldrich	418	2.06

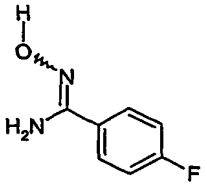
Intermediate 75		Astatech, or *J. Med. Chem.*, 1993, 36, 2300	431	2.18
Intermediate 76		*Synthesis*, 1971, 258; or WO 03/082190	401	2.35
Intermediate 77		*Eur. J. Med. Chem.*, 1992 37, 581	414	2.30
Intermediate 78		*Indian J. Chemistry*, 2002, 41B, 1093	413	2.24
Intermediate 79		Lancaster Synthesis	458	2.18

Intermediate 80: **(1*E/Z*)-*N*-hydroxy-2-(4-methyl-1-piperazinyl)ethanimidamide**



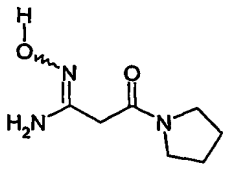
(4-Methyl-1-piperazinyl)acetonitrile (1.08g, 7.7mmol) (*J. Med. Chem.*, 1999, 42, 2870) was added to a suspension of potassium carbonate (3.2g, 23.1mmol) and hydroxylamine hydrochloride (1.06g, 15.4mmol) in ethanol (10ml). The reaction mixture was heated at reflux for 9 hours then allowed to cool. The reaction was filtered and the solvent evaporated in vacuo to afford Intermediate 80 (1.53g). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) 9.02 (br s, 1H), 5.17 (br s, 2H), 2.78 (s, 2H), 2.31 (br s , 8H), 2.13 (s, 3H).

Intermediate 81: 4-Fluoro-*N*-hydroxybenzenecarboximidamide



Commercially available from Sigma-Aldrich, CAS (Chemical Abstracts) Registry Number 22179-78-8.

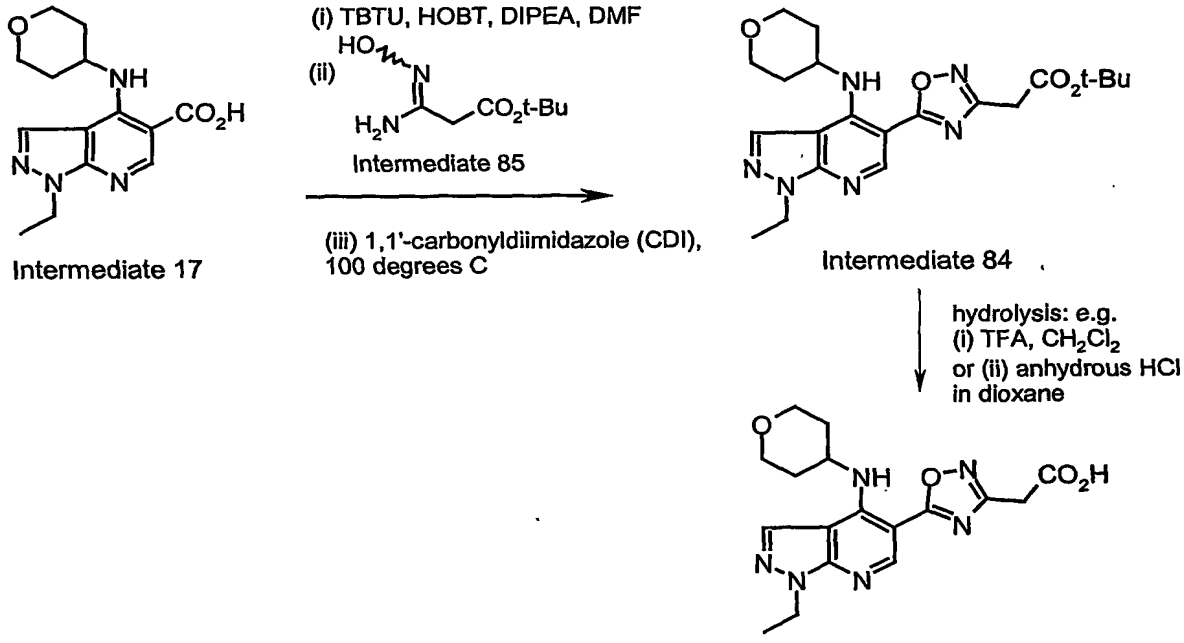
Intermediate 82: (1*E*/*Z*)-*N*-hydroxy-3-oxo-3-(1-pyrrolidinyl)propanimidamide



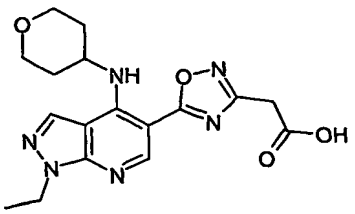
Commercially available from the Maybridge Chemical Company, CAS (Chemical Abstracts) Registry Number 57399-51-6.

Intermediates 83 and 84

The structures of Intermediates 83 and 84 and their preparation are as follows:

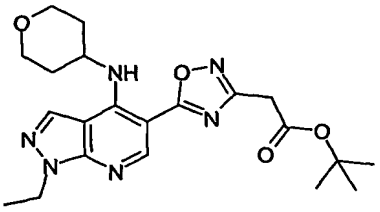


Intermediate 83: **{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}acetic acid**



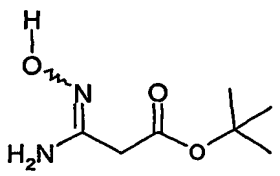
Anhydrous hydrogen chloride in dioxane (8ml, 4M solution) was added to Intemediate 84 (0.807g, 1.88mol). The reaction mixture was stirred overnight at room temperature then evaporated in vacuo. The residue was suspended in ether and the mixture filtered to give Intermediate 83 as a brown solid (0.525g). LCMS showed $MH^+ = 373$; $T_{RET} = 2.62$min.

Intermediate 84: **1,1-Dimethylethyl {5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}acetate**

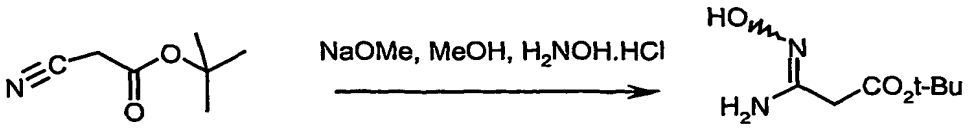


Diisopropyethylamine (8.3ml, 47.5mmol) was added to a mixture of Intermediate 17 (2.76g, 9.5mmol), TBTU (3.050g, 9.5mmol) and hydroxybenzotriazole (1.28g, 9.5mmol) in N,N-dimethylformamide (40ml) at room temperature. After stirring for 10 minutes Intermediate 85 (2.318g, 13.3mmol) was added. The reaction mixture was srirred for 50 minutes then 1,1'-carbonyldiimidazole (1.54g, 9.5mmol) was added and the reaction heated at 100 °C for 16 hours. The solvent was removed in vacuo and the residue partitioned between dichloromethane and water. The organic phase was washed with aqueous sodium hydrogen carbonate (5%) then dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by chromaography using the Biotage system (100g, silica) eluting with cyclohexane:ethyl acetate (1:1). Intermediate 84 was obtained a brown solid (0.97g). LCMS showed $MH^+ = 429$ $T_{RET} = 3.26$min.

Intermediate 85: **1,1-Dimethylethyl (3*E*/*Z*)-3-(hydroxyamino)-3-iminopropanoate**



The reaction scheme was as follows:

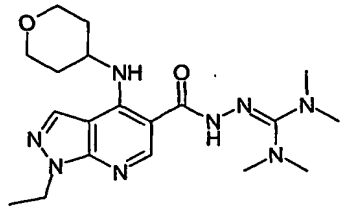


Available from Aldrich

Intermediate 85

A solution of sodium methoxide in methanol (50ml, 0.5M) was added to hydroxylamine hydrochloride (1.78g, 25.62mmol) at room temperature. After stirring for 15 minutes the solution was filtered and the filtrate added to t-butyl cyanoacetate (3.0g, 21.25mmol, available from Aldrich). The solution was refluxed for 1.75 hours then cooled and evaporated in vacuo. The residue was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic phases washed with brine, dried ($MgSO_4$) and evaporated in vacuo. The residue was suspended in cyclohexane: ether (1:1) then filtered to give Intermediate 85 as a white solid (1.883g). ^1H NMR (400MHz in $CDCl_3$, 27°C, δppm) 8.34 (br s, 1H), 5.05 (br s, 2H), 3.09 (s, 2H), 1.47 (s, 9H).

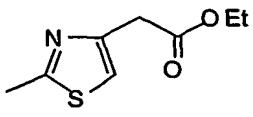
Intermediate 86: ***N*''-{[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}-*N*,*N*,*N*',*N*'-tetramethylcarbonohydrazonic diamide**



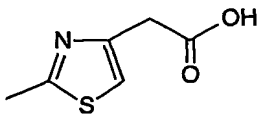
Intermediate 19 (0.1g, 0.29mmol), TBTU (0.094g, 0.29mmol) and diisopropylethylamine (0.204ml, 1.17mmol) in N,N-dimethylformamide (1ml) were stirred at room temperature for 1 hour. The solvent was evaporated in vacuo and the residue dissolved in methanol and applied to an SPE cartridge (aminopropyl, 5g). The cartridge was eluted with methanol and appropriate fractions evaporated in vacuo to give Intermediate 86 as a yellow solid (0.113g). LCMS showed $MH^+ = 403$; $T_{RET} = 1.99$min.

Intermediate 87: Ethyl (2-methyl-1,3-thiazol-4-yl) acetate

Prepared as described by K. Arakawa et. al., Chem Pharm Bull, 1972, **20** (5), 1041

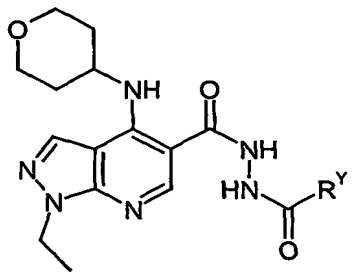


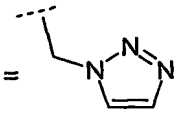
Intermediate 88: 2-Methyl-1,3-thiazol-4-yl acetic acid



To a solution of Intermediate 87 (6g, 32.4mmol) in dioxan (15ml) was added a solution of lithium hydroxide monohydrate (1.53g, 36.4mmol) in water (15ml). The mixture was stirred for 17h, then washed with diethyl ether (20ml), then with ethyl acetate (20ml) and acidified with concentrated hydrochloric acid under ethyl acetate (50ml). The combined aqueous phases were adjusted to pH 2.7 by addition of sodium bicarbonate and extracted with further ethyl acetate (2x50ml). The combined organic phases were washed with water (20ml) and saturated brine (20ml), then concentrated in vacuo to afford Intermediate 88 as a white solid (1.69g). ^{1}H NMR (400MHz in $CDCl_3$, 27°C, δppm) 2.74 (s, 3H), 3.85 (s, 2H), 5.8-6.2 (br, s, 1H), 7.02 (s, 1H).

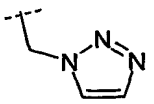
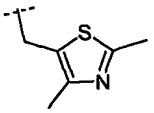
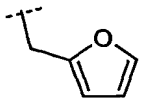
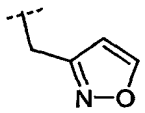
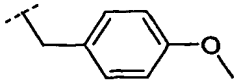
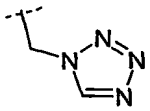
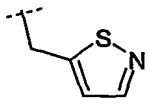
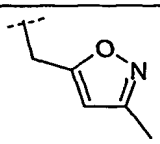
Intermediate 89: 1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*'-(1*H*-1,2,3-triazol-1-ylacetyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide

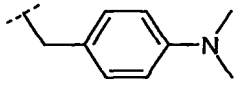
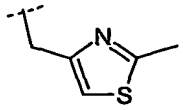
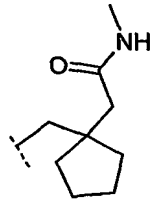
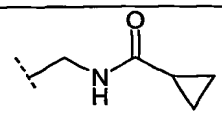
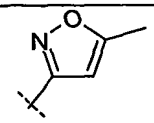
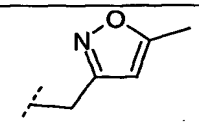
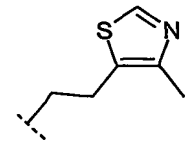
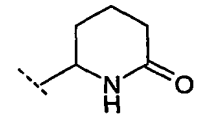
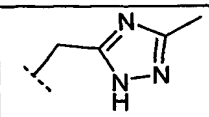
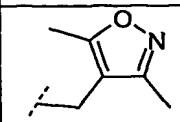


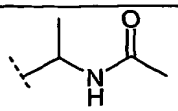
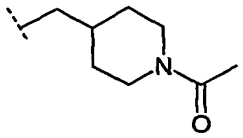
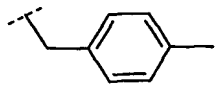
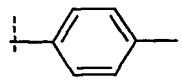
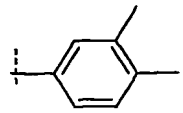
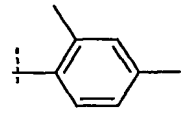
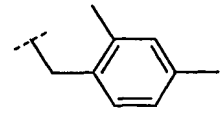
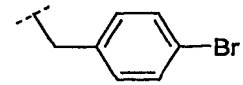
Intermediate 89, R^Y = 

General Procedure for Intermediates 89 to 114:

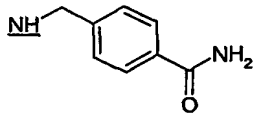
A mixture of carboxylic acid R^YCO_2H (0.2mmol), diisopropylethylamine (0.105ml, 0.6mmol) and TBTU (0.071g, 0.22mmol) in N,N-dimethylformamide (0.5ml) was allowed to stand for 10 minutes. A mixture of Intermediate 19 (0.2mmol) and diisopropylethylamine (0.035ml, 0.2mmol) in N,N-dimethylformamide (0.5ml) was added. After agitation the reactions were allowed to stand for 16 hours. The solvent was removed in vacuo and residue was applied to an SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted with chloroform, ethyl acetate:chloroform (1:1), ethyl acetate, ethyl acetate:methanol (9:1, 2ml). Appropriate fractions were evaporated in vacuo to afford the Intermediates below.

Intermediate Number	R^Y	Source of Carboxylic acid R^YCO_2H	MH^+	T_{RET} (min)
89		ChemPacific Ltd	413	2.17
90		SPECS Fleminglaan 16 2289 CP Rijswijk The Netherlands	457	2.3
91		Advanced Synthesis P.O. Box 437920 San Ysidro, California 92173 United States	412	2.4
92		Microchemistry Ltd, Shosse Entusiastov 56, Moscow 1111123, Russia	413	2.25
93		Aldrich	452	2.59
94		Maybridge Chemical Company Ltd., Trevillett, Tintagel, Cornwall PL34 0HW, United Kingdom	*414*	2.2
95		Described by R. Raap et. al., US3271407A	*429*	2.33
96		Aldrich	427	2.32

97		Aldrich	465	2.21
98		Intermediate 88	443	2.33
99		Peakdale Molecular Ltd, Peakdale Science Park, Sheffield Road, Chapel-en-le-Frith, High Peak SK23 0PG, UK	*485*	2.47
100		J. Chem. Soc., Perkin Trans II, 1993, 4, 741-8	*429*	2.19
101		Lancaster Synthesis	413	2.42
102		J. Chem. Soc. Perkin Trans. 1, 1976, 9, 994-7	*427*	2.35
103		Microchemistry Ltd, Shosse Entusiastov 56, Moscow 1111123, Russia	457	2.32
104		Microchemistry Ltd, Shosse Entusiastov 56, Moscow 1111123, Russia	429	2.13
105		Microchemistry Ltd, Shosse Entusiastov 56, Moscow 1111123, Russia	427	2.11
106		Microchemistry Ltd, Shosse Entusiastov 56, Moscow 1111123, Russia	441	2.35

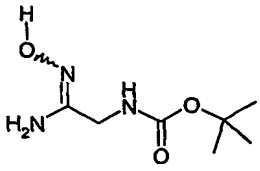
107		Sigma Chemical Company	*417*	2.11
108		T. J. Guzi et.al., WO 03/022835	471	2.22
109		Aldrich	437	2.7
110		Aldrich	423	2.6
111		Aldrich	437	2.8
112		Aldrich	437	2.7
113		ACB Blocks Ltd or Described by Rzeszotarski, W.J. in WO 93/05772	451	2.7
114		Aldrich	501 / 503	2.8

Intermediate 115: **4-(Aminomethyl)benzamide**



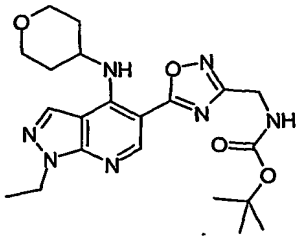
Can be prepared according to the procedure described by L.W.Jones *et. al.* WO 02/085860.

Intermediate 116: **1,1-Dimethylethyl [(2*Z*)-2-(hydroxyamino)-2-iminoethyl]carbamate**



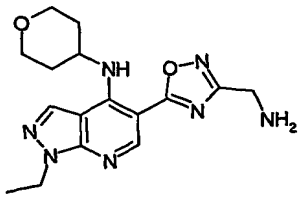
Prepared from commercially available N-(tert-Butoxycarbonyl)-2-aminoacetonitrile as decribed by M. Schwarz *et. al.* WO 02/102799.

Intermediate 117: 1,1-Dimethylethyl ({5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)carbamate



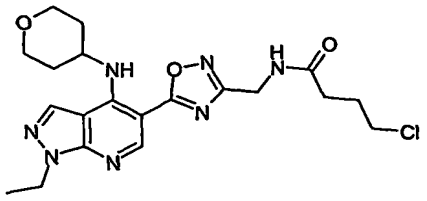
Diisopropylethylamine (6.0ml, 34.4mmol) was added to a stirred mixture of Intermediate 17 (2.0g, 6.89mmol), TBTU (2.212g, 6.89mmol) and HOBT (0.931g, 6.89mmol) in dry dimethylformamide (45ml). After 10min, the resulting clear solution was treated with Intermediate 116 (1.89g, 10mmol). The reaction mixture was stirred at room temperature for 2h. DBU (5.14ml, 34.5mmol) was added, and the reaction mixture was heated at 80°C. After 3.5h at 80°C, the reaction mixture was evaporated in vacuo, and the residue was dissolved in dichloromethane (150ml) and washed successively with 5% sodium hydrogen carbonate (50ml) and water (50ml). The organic solution was dried over anhydrous sodium sulphate and evaporated to give the crude product. Purification by Biotage chromatography (silica, 100g) eluting with ethyl acetate-petroleum ether (1:1) afforded Intermediate 117 as a white solid (2.70g). LCMS showed MH^+ =444, T_{RET} = 3.06min.

Intermediate 118: 5-[3-(Aminomethyl)-1,2,4-oxadiazol-5-yl]-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine



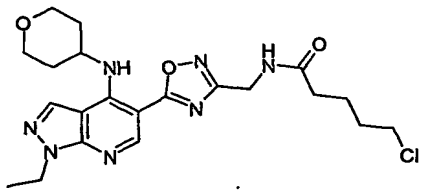
Trifluoroacetic acid (5ml) was added to a stirred solution of Intermediate 117 (1.774g, 4.0mmol) in dry dichloromethane (20ml) at 0°C. After 2h, the reaction mixture was neutralised by careful addition of 5% sodium hydrogen carbonate solution (150ml) and solid sodium hydrogen carbonate. The resulting mixture was extracted with chloroform (2 x 100ml). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated to afford Intermediate 118 as a white solid (1.358g). LCMS showed MH^+ =344, T_{RET} = 1.95min.

Intermediate 119: 4-Chloro-*N*-({5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)butanamide



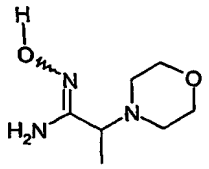
4-chlorobutanoyl chloride (0.12mmol) was added to a stirred solution of Intermediate 118 (0.1mmol) and diisopropylethylamine (0.3mmol) in chloroform (1ml) at room temperature. After stirring at room temperature for 16h, the reaction mixture was applied to a SPE cartridge (aminopropyl, 2g) and the cartridge was eluted sequentially with chlororm, ethyl acetate and methanol. Fractions containing the desired product were combined and blown down under nitrogen. The resulting residue was further purified on a SPE cartidge (silica, 1g) eluting with a gradient of 30-100% ethyl acetate in petroleum ether to afford Intermediate 119 as a white solid (45mg).). LCMS showed MH^+ =448, T_{RET} = 2.77min.

Intermediate 120: 5-Chloro-*N*-({5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)pentanamide



5-chloropentanoyl chloride (0.12mmol) was added to a stirred solution of Intermediate 118 (0.1mmol) and diisopropylethylamine (0.3mmol) in chloroform (1ml) at room temperature. After stirring at room temperature for 16h, the reaction mixture was applied to a SPE cartridge (aminopropyl, 2g) and the cartridge was eluted sequentially with chlororm, ethyl acetate and methanol. Fractions containing the desired product were combined and blown down under nitrogen. The resulting residue was further purified on a SPE cartidge (silica, 1g) eluting with a gradient of 30-100% ethyl acetate in petroleum ether to afford Intermediate 120 as a white solid (46mg). LCMS showed MH^+ =462, T_{RET} = 2.86min.

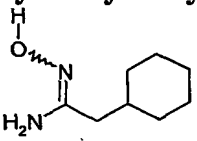
Intermediate 121: (1*E*/*Z*)-*N*-hydroxy-2-(4-morpholinyl)propanimidamide



Prepared from α–methyl-4-morpholineacetonitrile using a similar process to that described for any of Intermediates 9, 22 or 80 using similar or the same number of moles of reagents and/or volumes of solvents. 1H NMR (27 °C, d4-MeOH) 3.70-3.60 (m, 5H), 3.13-3.07 (m, 2H), 2.83-2.76 (m, 2H), 1.84 (d, J = 5Hz, 3H)

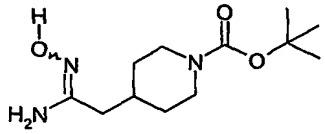
α–Methyl-4-morpholineacetonitrile can be prepared according to the procedure described by H.R.Henze *et. al.* J. Am. Chem. Soc 1957, 79, 6230.

Intermediate 122: (1*E*/*Z*)-2-cyclohexyl-*N*-hydroxyethanimidamide



Can be prepared from cyclohexylacetic acid (commercially available from e.g. Aldrich) according to the procedure described by T.R. Alessi *et al.*in US 4895860.

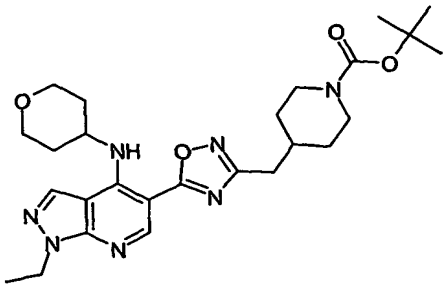
Intermediate 123: 1,1-Dimethylethyl 4-[(2*Z*)-2-(hydroxyamino)-2-iminoethyl]-1-piperidinecarboxylate



Prepared from 1,1-dimethylethyl 4-(cyanomethyl)-1-piperidinecarboxylate using a similar process to that described for any of Intermediates 9, 22 or 80 using similar or the same number of moles of reagents and/or volumes of solvents.

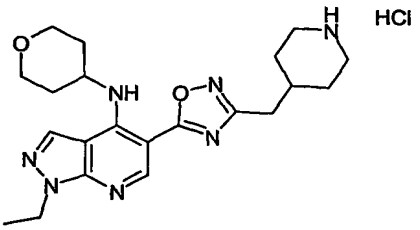
1,1-dimethylethyl 4-(cyanomethyl)-1-piperidinecarboxylate can be prepared from commercially available 1,1-dimethylethyl 4-oxo-1-piperidinecarboxylate according to the procedure described by A.M.Wilson in WO 00/006159.

Intermediate 124: 1,1-Dimethylethyl 4-({5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-1-piperidinecarboxylate



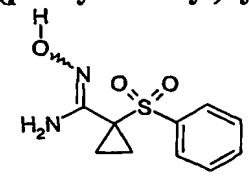
A mixture of Intermediate 16 (0.064g, 0.2mmol), Intermediate 80 (0.257g, 1mmol), a solution of sodium ethoxide in EtOH (0.19ml, 21% solution) and powdered 4Å molecular sieves (0.38g) in EtOH (2ml) were stirred at 82 °C under an atmosphere of nitrogen for 18 hours. Additional sodium ethoxide in ethanol (0.19ml, 21% solution), molecular sieves (0.38g) and ethanol (4ml) were added and the reaction heated for a further 72 hours. The reaction mixture was filtered, the solvent was evaporated in vacuo and the residue was applied to an SPE cartridge (silica, 2g). The cartridge was eluted with cyclohexane: ethyl acetate (4:1, 2:1, 1:1), then ethyl acetate to afford Intermediate 124 as a colourless oil (0.052g). LCMS showed $MH^+ = 512$; $T_{RET} = 3.51$min.

Intermediate 125: 1-Ethyl-5-[3-(4-piperidinylmethyl)-1,2,4-oxadiazol-5-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine hydrochloride



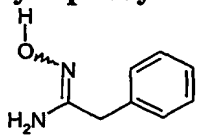
A solution of hydrogen chloride in dioxane (1ml) was added to Intermediate 124 (0.052g, 0.1mmol) and the reaction mixture stirred at 20 °C for 2 hours. The solution was evaporated in vacuo to afford Intermediate 125 as a yellow solid (0.047g). LCMS showed $MH^+ = 412$; $T_{RET} = 2.21$min.

Intermediate 126: *N*-Hydroxy-1-(phenylsulfonyl)cyclopropanecarboximidamide



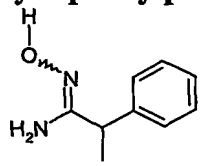
Prepared from 1-(phenylsulphonyl)cyclopropoanecarbonitrile (commercially available from Menai Organics Ltd, Menai Technology Centre, Deiniol Roas, Bangor, Gwynedd, Wales, LL57 UP, United Kingdom or described in Bull. Chem. Soc. Jpn. 1985 58(2), 765) using a similar process to that described for any of Intermediates 9, 22 or 80 using similar or the same number of moles of reagents and/or volumes of solvents. LCMS showed $MH^+ = 241$; $T_{RET} = 1.71$min.

Intermediate 127: (1*E/Z*)-*N*-Hydroxy-2-phenylethanimidamide



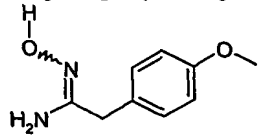
Commercially available from Maybridge Chemical Company Ltd, Trevillett, Tintagel, Cornwall, PL34 0HW, United Kingdom.

Intermediate 128: (*1E/Z*)-*N*-Hydroxy-2-phenylpropanimidamide



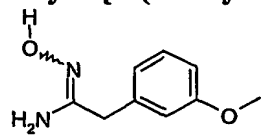
Can be prepared from a-methylphenylacetonitirile according to the procedure described by J. Rheineimer EP 323864.

Intermediate 129: (*1E/Z*)-*N*-Hydroxy-2-[4-(methyloxy)phenyl]ethanimidamide



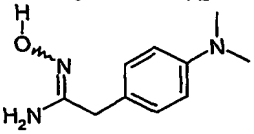
Commercially available from Exploratory Library, Ambinter, 46 quai Louis Bleriot, Paris, F-75016, France.

Intermediate 130: (*1E/Z*)-*N*-Hydroxy-2-[3-(methyloxy)phenyl]ethanimidamide



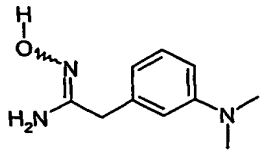
Can be prepared from according to the procedure described by S.Borg et. Al European J.Med Chem. 1993, 28(10,) 801.

Intermediate 131: (*1E/Z*)-2-[4-(Dimethylamino)phenyl]-*N*-hydroxyethanimidamide



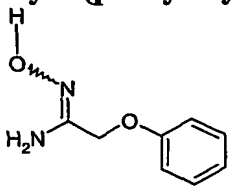
Prepared from 4-(dimethylamino)benzeneacetonitrile (described by Borovicka *et al.* Collect. Czech. Chem. Commun 1955, 20, 437) using a similar process to that described for any of Intermediates 9, 22 or 80 using similar or the same number of moles of reagents and/or volumes of solvents. LCMS showed $MH^+ = 194$; $T_{RET} = 0.38$min.

Intermediate 132: (*1E/Z*)-2-[3-(Dimethylamino)phenyl]-*N*-hydroxyethanimidamide



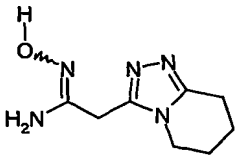
Prepared from 3-(dimethylamino)benzeneacetonitrile (described by M.L. Sznaidman *et al.* Bioorganic Medicinal Chemistry Letters 1996, 6(5), 565) using a similar process to that described for any of Intermediates 9, 22 or 80 using similar or the same number of moles of reagents and/or volumes of solvents. LCMS showed MH^+ = 194; T_{RET} = 0.46min

Intermediate 133: (*1E/Z*)-*N*-Hydroxy-2-(phenyloxy)ethanimidamide



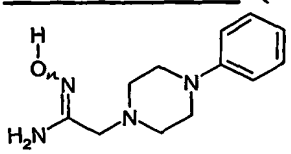
Commercially available from Pfaltz & Bauer Inc.

Intermediate 134: (*1E/Z*)-*N*-hydroxy-2-(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)ethanimidamide



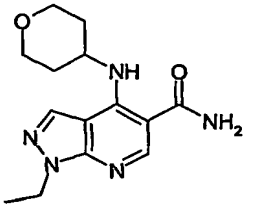
Prepared from 5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyridine-3-acetonitrile (commercially available from Interchim, 213 Avenue Kennedy, BP 1140, Montlucon, Cedex 03103, France or Exploratory Library, Ambinter, 46 quai Louis Bleriot, Paris, F-75016, France) using a similar process to that described for any of Intermediates 9, 22 or 80 using similar or the same number of moles of reagents and/or volumes of solvents. LCMS showed MH^+ = 198; T_{RET} = 0.32min.

Intermediate 135: (*1E/Z*)-*N*-Hydroxy-2-(4-phenyl-1-piperazinyl)ethanimidamide



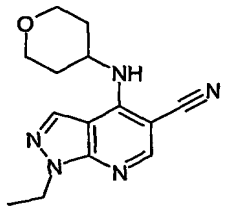
Prepared from 4-phenyl-1-piperazineacetonitrile (commercially available from Interchim, 213 Avenue Kennedy, BP 1140, Montlucon, Cedex 03103, France or Exploratory Library, Ambinter, 46 quai Louis Bleriot, Paris, F-75016, France) using a similar process to that described for any of Intermediates 9, 22 or 80 using similar or the same number of moles of reagents and/or volumes of solvents. LCMS showed MH^+ = 235; T_{RET} = 1.09min.

Intermediate 136: 1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide



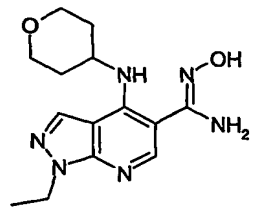
A solution of Intermediate 17 (3.263g, 11.25mmol) in thionyl chloride (17ml) was heated at 60 °C for 2 hours. The solution was concentrated in vacuo and then co-evaporated with dichloromethane. The residue was suspended in a solution of ammonia in dioxane (45ml, 0,5M solution) and the resultant mixture stirred for 18 hours. After concentration in vacuo the residue was re-suspended in ammonia in dioxane (45ml, 0.5M) and stirred for a further 16 hours. The solvent was removed in vacuo and the solid suspended in a mixture of dichloromethane (40ml) and water (40ml). The solid was filtered, washed with water and dried in vacuo over P_2O_5 to afford Intermediate 136 as a cream solid (2.50g). LCMS showed $MH^+ = 290$; $T_{RET} = 2.12$min

Intermediate 137: 1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile



Burgess Reagent 4.53g, 19.0mmol) was added to a suspension of Intermediate 136 (5.0g, 17.3mmol) in THF (80ml). The reaction mixture was stirred at room temperature for 18 hours then a further portion of Burgess Reagent (0.9g, 1.8mmol) was added and stirring continued for 5 hours. The reaction mixture was concentrated in vacuo and the residue partitioned between dichloromethane and water. The organic phase was washed with water, dried and evaporated in vacuo to afford Intermediate 137 as an off-white solid (4.43g). LCMS showed $MH^+ = 272$; $T_{RET} = 2.40$min

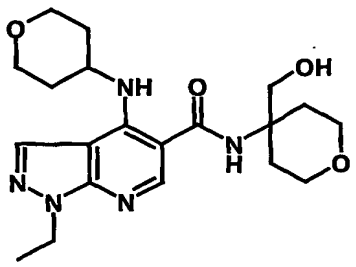
Intermediate 138: 1-Ethyl-*N*-hydroxy-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboximidamide



Intermediate 137 (3.50g, 12.9mmol), hydroxylamine hydrochloride (3.30g, 47.8mmol) and sodium hydrogencarbonate (4.01g, 47.8mmol) in EtOH (45ml) were heated at 45 °C

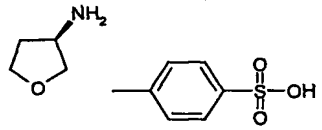
for 1.5 hours then at 50 °C for 2.5 hours. The suspension was concentrated in vacuo and the solid stirred in dichloromethane (80ml) for 0.5 hours. The mixture was filtered and the solid stirred in EtOH, the resultant mixture was filtered and the filtrate evaporated. The solid was then washed with dichloromethane three time to afford Intermediate 138 as a white solid (1.62g). LCMS showed $MH^+ = 305$; $T_{RET} = 1.85$min

Intermediate 139: 1-Ethyl-*N*-[4-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

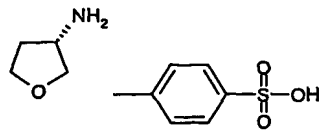


Intermediate 139 was prepared from Intermediate 17 and (4-aminotetrahydro-2*H*-pyran-4-yl)methanol (commercially available from PharmaCore Inc., 4170 Mendenhall Oaks Pkwy, Suite 140, High point, NC, USA) using an analogous method to that for Intermediate 42. LCMS showed $MH^+ = 404$, $T_{RET} = 2.19$min.

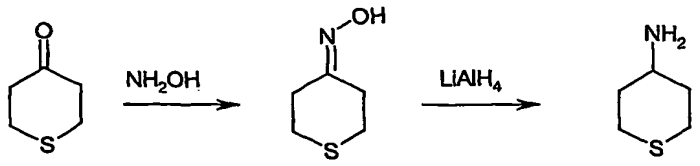
Intermediate 140: (R)-(+)-3-Amino tetrahydrofuran 4-toluenesulphonate
Commercially available from Fluka Chemie AG, Germany (CAS 111769-27-8)



Intermediate 141: (S)-(-)-3-Amino tetrahydrofuran 4-toluenesulphonate
Commercially available from E. Merck, Germany; or from E. Merck (Merck Ltd), Hunter Boulevard, Magna Park, Lutterworth, Leicestershire LE17 4XN, United Kingdom (CAS 104530-80-5)

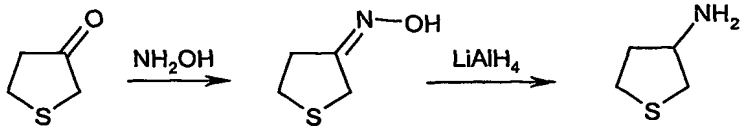


Intermediate 142: Tetrahydro-2H-thiopyran-4-amine
Prepared from commercially available tetrahydrothiopyran-4-one as described by Subramanian et. al., *J. Org. Chem.*, 1981, 46, 4376-4383. Subsequent preparation of the hydrochloride salt can be achieved by conventional means.



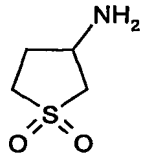
Intermediate 143: Tetrahydro-3-thiopheneamine

Prepared in an analogous manner to Intermediate 142 from commercially available tetrahydrothiophene-4-one. The oxime formation is described by Grigg et.al., *Tetrahedron*, 1991, 47, 4477-4494 and the oxime reduction by Unterhalt et. al., *Arch. Pharm.*, 1990, 317-318.



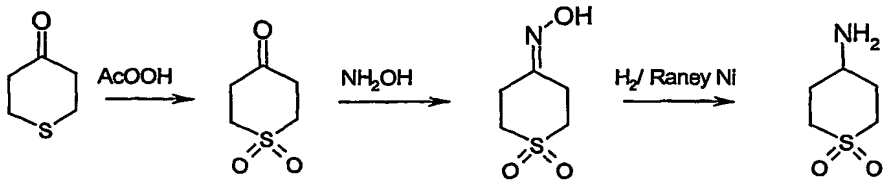
Intermediate 144: Tetrahydro-3-thiopheneamine 1,1-dioxide hydrochloride

Commercially available from Sigma Aldrich Library of Rare Chemicals (SALOR) (CAS-6338-70-1). Preparation of the hydrochloride salt of the amine can be achieved by conventional means.

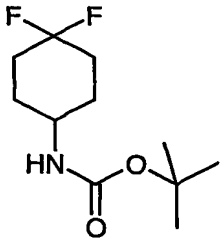


Intermediate 145: Tetrahydro-2H-thiopyran-4-amine-1,1-dioxide hydrochloride

Prepared in an analogous manner to Intermediate 11 from commercially available tetrahydrothiophene-4-one. Oxidation to 1,1-dioxo-tetrahydro-1λ^6-thiopyran-4-one is described by Rule et. al., in *J. Org. Chem.*, 1995, 60, 1665-1673. Oxime formation is described by Truce et.al., in *J. Org. Chem.*, 1957, 617, 620 and oxime reduction by Barkenbus et. al., *J. Am. Chem. Soc.*, 1955, 77, 3866. Subsequent preparation of the hydrochloride salt of the amine can be achieved by conventional means.

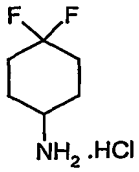


Intermediate 146: 1,1-Dimethylethyl (4,4-difluorocyclohexyl)carbamate



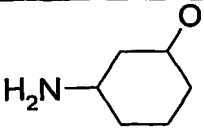
(Diethylamino)sulphur trifluoride (DAST), (0.06ml, 0.47mmol), was added to a stirred solution of 1,1-dimethylethyl(4-oxocyclohexyl)carbamate, (250mg, 1.17mmol, commercially available from AstaTech Inc., Philadelphia, USA) in anhydrous dichloromethane (5ml) and the mixture was stirred under nitrogen at 20°C. After 22h, the reaction mixture was cooled to 0°C, treated with saturated sodium hydrogen carbonate solution (4ml), and then allowed to warm to ambient temperature. The phases were separated by passage through a hydrophobic frit and the aqueous phase was further extracted with DCM (5ml). The combined organic phases were concentrated in vacuo to give an orange solid (369mg) which was further purified by chromatography using a SPE cartridge (silica, 10g), eluting with DCM to afford Intermediate 62 (140mg) containing 20% of **1,1-dimethylethyl (4-fluoro-3-cyclohexen-1-yl)carbamate.** ^{1}H NMR (400MHz in $CDCl_3$, 27°C, δppm)
Minor component: δ5.11 (dm, 16Hz, 1H), 4.56 (br, 1H), 3.80 (br, 1H) 2.45-1.45 (m's, 6H excess), 1.43 (s, 9H). Major component: δ4.43 (br, 1H), 3.58 (br, 1H), 2.45-1.45 (m's, 8H excess), 1.45 (s, 9H).

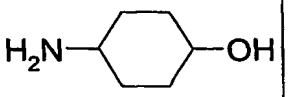
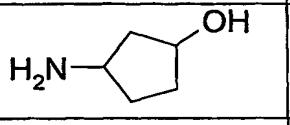
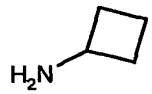
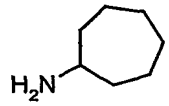
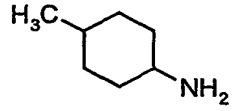
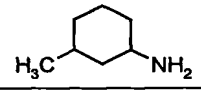
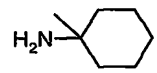
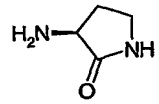
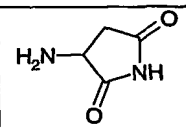
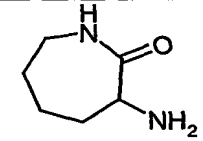
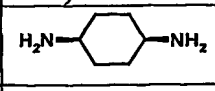
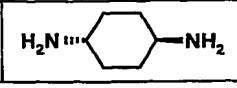
Intermediate 147: (4,4-Difluorocyclohexyl)amine hydrochloride

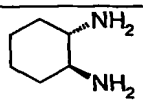
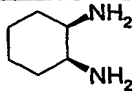
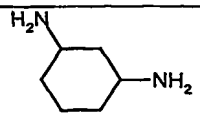


A solution of hydrogen chloride in dioxane (4M, 1.6ml) was added at 20°C to a stirred solution of Intermediate 146 (140mg, 0.6mmol), in dioxane (1.6ml). After 3h, the reaction mixture was concentrated in vacuo to afford Intermediate 147 (96.5mg) containing **4-fluoro-3-cyclohexen-1-amine.** ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) Minor component: δ8.22 (br, 3H excess), 5.18 (dm, 16Hz, 1H), 3.28-3.13 (m, 1H excess), 2.41-1.53 (m's, 6H excess). Major component: δ8.22 (br, 3H excess), 3.28-3.13 (m, 1H excess), 2.41-1.53 (m's, 8H excess). Impurities are also present.

Intermediates 148 to 163: different types of $R^3R^{3a}NH$

Intermediate Number	$R^3R^{3a}NH$	Source of $R^3R^{3a}NH$
148		*J. Chem. Soc., Perkin Trans. 1,* 1994, 537

148A	as Intermediate 148, but racemic *cis*-isomer, i.e. racemic *cis*-(3-hydroxy-cyclohex-1-yl)-amine	*J. Chem. Soc., Perkin Trans 1,* 1994, 537
149		Aldrich; or TCI-America
150		US 4219660
151		Aldrich
152		Aldrich
153		Aldrich
154		Pfaltz-Bauer
155		*J. Org. Chem.*, 1985, 50(11), 1859
156		WO 99/12933
157		EP 1188744
158	 (3-Aminoazepan-2-one)	Sigma-Aldrich Company Ltd
159 *		*J. Med. Chem.*, 1994, 37(17), 2360
160 *		Aldrich

161 *		Aldrich
162 *		Aldrich
163 *		Peakdale Molecular Ltd

* For $R^3R^{3a}NH$ in Intermediates 159-163, $R^3R^{3a}NH$ is the *cis* or *trans* isomer, if shown. For Intermediates 161-163, $R^3R^{3a}NH$ is usually the 3-amino- or 2-amino-cyclohex-1-ylamine in a racemic form.

Table of Examples

Example Number	Name
1	N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
2	N-Cyclopentyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
3	N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
4	N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
5	N-Cyclopentyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-thiadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
6	N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
7	1-Ethyl-N-(4-fluorophenyl)-5-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
8	N-Cyclopentyl-5-(1,3-dimethyl-1H-1,2,4-triazol-5-yl)-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine
9	1-Ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
10	N-Cyclohexyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
11	1-Ethyl-N-isobutyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
12	1-Ethyl-N-isobutyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
13	N-Cyclohexyl-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
14	1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine also named: 1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
15	N-[(1R)-1,2-dimethylpropyl]-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
16	N-[(1S)-1,2-dimethylpropyl]-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
17	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine also named: 5-[5-(1,1-Dimethylethyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
18	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-cyclohexyl-1-ethyl-1H-pyrazolo[3,4-

	b]pyridin-4-amine
19	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine
20	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-isobutyl-1H-pyrazolo[3,4-b]pyridin-4-amine
21	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-[(1S)-1,2-dimethylpropyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine
22	5-(5-Tert-butyl-1,3,4-oxadiazol-2-yl)-N-[(1R)-1,2-dimethylpropyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine
23	1-Ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
24	N-Cyclohexyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
25	1-Ethyl-N-isobutyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
26	N-[(1S)-1,2-dimethylpropyl]-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
27	N-[(1R)-1,2-dimethylpropyl]-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-oxadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine
28	1-Ethyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
29	1-Ethyl-5-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
30	5-{3-[(Dimethylamino)methyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
31	1-Ethyl-5-[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
32	5-(5-Cyclopropyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
33	N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
34	1-Ethyl-5-[5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
35	1-Ethyl-5-{5-[(4-methylpiperazin-1-yl)methyl]-1,3,4-oxadiazol-2-yl}-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine also named: 1-Ethyl-5-{5-[(4-methyl-1-piperazinyl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
36	5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-isopropyl-1,3,4-oxadiazole-2-carboxamide
37	4-{5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}-1-methylpyrrolidin-2-one
38	1-Ethyl-N-tetrahydro-2H-pyran-4-yl-5-(5-tetrahydro-2H-pyran-4-yl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine

	also named: 1-Ethyl-N-(tetrahydro-2H-pyran-4-yl)-5-[5-(tetrahydro-2H-pyran-4-yl)-1,3,4-oxadiazol-2-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine
39	1-Ethyl-5-[5-(morpholin-4-ylmethyl)-1,3,4-oxadiazol-2-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine also named: 1-Ethyl-5-[5-(morpholin-4-ylmethyl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
40	5-[5-(Tert-butoxymethyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
40A	Methyl 2-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-4,5-dihydro-1,3-oxazole-4-carboxylate
41	Methyl 2-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3-oxazole-4-carboxylate
42	1-Ethyl-5-(4-methyl-4,5-dihydro-1,3-oxazol-2-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
43	1-(n-Propyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
44	1-Ethyl-5-[5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
45	1-Ethyl-5-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
46	1-Ethyl-5-(5-methyl-1,2,4-triazol-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
47	N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
48	N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine
49	1-Ethyl-5-[(4R)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
50	1-Ethyl-5-[(4S)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
51	1-Ethyl-5-[(4S)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
52	1-Ethyl-5-[(4R)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
53	1-Ethyl-5-[(4S,5R)-5-methyl-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
54	1-Ethyl-5-[(5R)-5-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
55	1-Ethyl-5-[(5S)-5-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
56	5-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
57	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-

	b]pyridin-5-yl]-1,3-oxazole-4-carboxylic acid
58	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-(1-methylethyl)-1,3-oxazole-4-carboxamide
59	1-Ethyl-5-[4-(4-morpholinylcarbonyl)-1,3-oxazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
60	1-Ethyl-N-methyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
61	*trans*-4-{[1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl]amino}cyclohexanol
62	1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(tetrahydro-2H-pyran-3-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
63	4-{[1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl]amino}cyclohexanone
64	1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-n-propyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
65	5-[5-(1,1-Dimethylethyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-6-methyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
66	1-Ethyl-6-methyl-N-(tetrahydro-2H-pyran-4-yl)-5-[5-(tetrahydro-2H-pyran-4-yl)-1,3,4-oxadiazol-2-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine
67	5-(5-Cyclobutyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
68	5-{5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}-2-pyrrolidinone
69	N-({5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}methyl)acetamide
70	1-Ethyl-5-[5-(1-methyl-2-piperidinyl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
71	1-Ethyl-5-{5-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-1,3,4-oxadiazol-2-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
72	3-{5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}cyclopentanone
73	1-Ethyl-5-[5-(tetrahydro-3-furanyl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
74	(4S)-4-{5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}-1,3-thiazolidin-2-one
75	5-[5-(2,2-Dimethylcyclopropyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
76	N-({5-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}methyl)-N-methylacetamide
77	1-Ethyl-N-(tetrahydro-2H-pyran-4-yl)-5-[5-(tetrahydro-2H-pyran-4-ylmethyl)-1,3,4-oxadiazol-2-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine
78	1-Ethyl-5-[5-(1-methylcyclobutyl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-

	2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
79	1-Ethyl-5-[5-(3-methyl-5-isoxazolyl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
80	1-Ethyl-5-[5-(1-methyl-1H-pyrazol-5-yl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
81	5-[5-(1-Acetyl-4-piperidinyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
82	1-Ethyl-5-{3-[(4-methyl-1-piperazinyl)methyl]-1,2,4-oxadiazol-5-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
83	1-Ethyl-5-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
84	1-Ethyl-5-{3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1,2,4-oxadiazol-5-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine
85	2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-phenylacetamide
86	2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-(1-phenylethyl)acetamide
87	1-Ethyl-5-{3-[2-oxo-2-(1-piperidinyl)ethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
88	2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-(phenylmethyl)acetamide
89	2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*,*N*-dimethylacetamide
90	*N*-Ethyl-2-{5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}acetamide
92	1-Ethyl-5-{3-[1-(4-morpholinyl)ethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
93	5-[3-(Cyclohexylmethyl)-1,2,4-oxadiazol-5-yl]-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
95	1-Ethyl-5-{3-[2-oxo-2-(1-piperidinyl)ethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
96	1-ethyl-5-{3-[2-(4-methyl-1-piperazinyl)-2-oxoethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
97	1-Ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-5-[5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3,4-oxadiazol-2-yl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
98	5-{5-[(2,4-Dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine formate
99	1-Ethyl-5-[5-(2-furanylmethyl)-1,3,4-oxadiazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine formate
100	1-Ethyl-5-[5-(3-isoxazolylmethyl)-1,3,4-oxadiazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine formate
103	1-ethyl-5-(5-{[4-(methyloxy)phenyl]methyl}-1,3,4-oxadiazol-2-yl)-*N*-

	(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine trifluoroacetate
104	1-Ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-5-[5-(1*H*-tetrazol-1-ylmethyl)-1,3,4-oxadiazol-2-yl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine formate
105	1-Ethyl-5-[5-(5-isothiazolylmethyl)-1,3,4-oxadiazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
106	1-Ethyl-5-{5-[(3-methyl-5-isoxazolyl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine formate
107	5-(5-{[4-(Dimethylamino)phenyl]methyl}-1,3,4-oxadiazol-2-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine (1:1)
108	1-Ethyl-5-{5-[(2-methyl-1,3-thiazol-4-yl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine formate
109	2-[1-({5-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}methyl)cyclopentyl]-*N*-methylacetamide trifluoroacetate
111	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}methyl)cyclopropanecarboxamide
112	1-Ethyl-5-{5-[(5-methyl-3-isoxazolyl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine formate
113	1-Ethyl-5-{5-[(5-methyl-3-isoxazolyl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
114	1-Ethyl-5-{5-[2-(4-methyl-1,3-thiazol-5-yl)ethyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine formate
117	5-{5-[(3,5-Dimethyl-4-isoxazolyl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine trifluoroacetate
118	*N*-(1-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}ethyl)acetamide
119	5-{5-[(1-acetyl-4-piperidinyl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine trifluoroacetate
120	1-Ethyl-5-{5-[(4-methylphenyl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
121	1-Ethyl-5-[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
122	5-[5-(3,4-Dimethylphenyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
123	5-[5-(2,4-Dimethylphenyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
125	5-{5-[(4-Bromophenyl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-

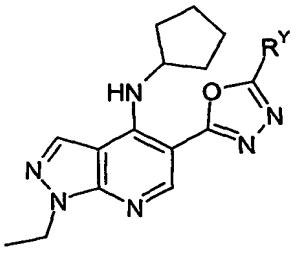
	(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
126	2-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-*N*-(phenylmethyl)-1,3-oxazole-4-carboxamide
127	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-{[4-(methyloxy)phenyl]methyl}-1,3-oxazole-4-carboxamide
128	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-[(2-methylphenyl)methyl]-1,3-oxazole-4-carboxamide
129	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-[(4-methylphenyl)methyl]-1,3-oxazole-4-carboxamide
130	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-[(3-methylphenyl)methyl]-1,3-oxazole-4-carboxamide
131	N-[(4-Chlorophenyl)methyl]-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide
132	N-[(2,3-Dimethylphenyl)methyl]-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide
133	N-[(3,5-Dimethylphenyl)methyl]-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide
134	N-[(3,4-Dimethylphenyl)methyl]-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide
135	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-(1-phenylethyl)-1,3-oxazole-4-carboxamide
136	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-{(1R)-1-[4-(methyloxy)phenyl]ethyl}-1,3-oxazole-4-carboxamide
137	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-[(1R)-1-phenylpropyl]-1,3-oxazole-4-carboxamide
138	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-(4-methylphenyl)-1,3-oxazole-4-carboxamide
139	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-({4-[(methylsulfonyl)amino]phenyl}methyl)-1,3-oxazole-4-carboxamide
140	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-{[4-(methylsulfonyl)phenyl]methyl}-1,3-oxazole-4-carboxamide
141	N-(1-Acetyl-4-piperidinyl)-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide
142	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-(tetrahydro-2H-pyran-4-yl)-1,3-oxazole-4-carboxamide

143	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-(tetrahydro-2-furanylmethyl)-1,3-oxazole-4-carboxamide
144	2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-[2-(4-methyl-1-piperazinyl)ethyl]-1,3-oxazole-4-carboxamide
145	N-[1-(Aminomethyl)cyclohexyl]-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-methyl-1,3-oxazole-4-carboxamide
146	N-(2,6-Dimethylphenyl)-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide
147	N-{[4-(Aminocarbonyl)phenyl]methyl}-2-[1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxamide
148	2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)acetamide
149	5-{3-[2-(2,6-Dimethyl-4-morpholinyl)-2-oxoethyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
150	1-Ethyl-5-{3-[2-(4-methyl-1-piperidinyl)-2-oxoethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
152	2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-[1-methyl-2-(methyloxy)ethyl]acetamide
153	5-{3-[2-(3,5-Dimethyl-1-piperidinyl)-2-oxoethyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
154	1-Ethyl-5-{3-[2-(3-methyl-1-piperidinyl)-2-oxoethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
155	2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-3-pyridinylacetamide
157	6-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}-2-piperidinone
158	1-Ethyl-5-{5-[(3-methyl-1*H*-1,2,4-triazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
159	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)acetamide
160	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)benzamide
161	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-phenylacetamide
162	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-

	b]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-methylpropanamide
163	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-3-methylbutanamide
164	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)cyclohexanecarboxamide
165	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-furancarboxamide
166	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)methanesulfonamide
167	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)benzenesulfonamide
168	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-1-phenylmethanesulfonamide
169	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-propanesulfonamide
170	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-1-propanesulfonamide
171	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)cyclopropanesulfonamide
172	*N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-thiophenesulfonamide
173	1-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-pyrrolidinone
174	1-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-piperidinone
175	5-{3-[(1-Acetyl-4-piperidinyl)methyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
176	1-Ethyl-5-(3-{[1-(3-methylbutanoyl)-4-piperidinyl]methyl}-1,2,4-oxadiazol-5-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
177	1-Ethyl-5-(3-{[1-(methylsulfonyl)-4-piperidinyl]methyl}-1,2,4-oxadiazol-5-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
178	1-Ethyl-5-{3-[1-(phenylsulfonyl)cyclopropyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
179	1-Ethyl-5-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
180	1-Ethyl-5-[3-(1-phenylethyl)-1,2,4-oxadiazol-5-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
181	1-Ethyl-5-(3-{[4-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
182	5-(3-{[4-(Dimethylamino)phenyl]methyl}-1,2,4-oxadiazol-5-yl)-1-

	ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
183	5-(3-{[3-(Dimethylamino)phenyl]methyl}-1,2,4-oxadiazol-5-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
184	5-(3-{[4-(Dimethylamino)phenyl]methyl}-1,2,4-oxadiazol-5-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
185	1-Ethyl-5-{3-[(phenyloxy)methyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
186	1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-5-[3-(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridin-3-ylmethyl)-1,2,4-oxadiazol-5-yl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
187	1-Ethyl-5-{3-[(4-phenyl-1-piperazinyl)methyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
188	1-Ethyl-5-(5-ethyl-1,2,4-oxadiazol-3-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
189	5-(5-{[4-(Dimethylamino)phenyl]methyl}-1,2,4-oxadiazol-3-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
190	1-Ethyl-5-(5-{[4-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
191	5-(3,8-Dioxa-1-azaspiro[4.5]dec-1-en-2-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine

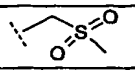
Example 1: N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



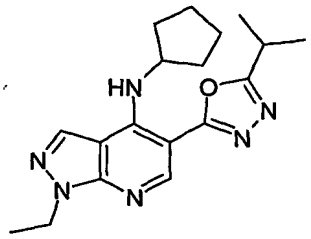
Example 1 R^Y = Me

Intermediate 4 (0.043g) was dissolved in acetonitrile (2ml) then treated with phosphorous oxychloride (0.101g) and stirred under nitrogen and heated at 90°C for 2h. The mixture was concentrated in vacuo and the residue partitioned between DCM and saturated aqueous sodium bicarbonate solution. The organic layer was concentrated in vacuo and applied to an SPE cartridge (aminopropyl, 1g), which was eluted with methanol. Concentration in vacuo afforded Example 1 (0.032g). LCMS showed $MH^+ = 313$; $T_{RET} = 3.13$min.

Similarly prepared, for example without limitation using the same or similar number of moles of reagents and/or volumes of solvents, but with an extended reaction time (see table) was:

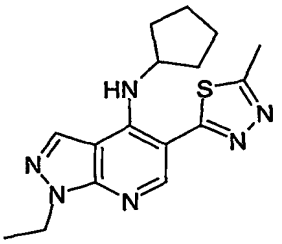
	R^Y	Starting material	Reaction time	MH^+ ion	T_{RET}(min)
Example 2		Intermediate 5	3h	391	2.88

Example 3: N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



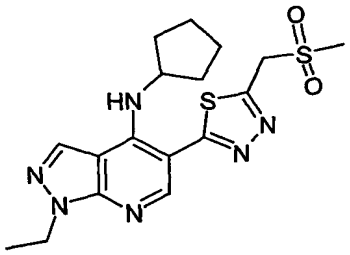
Intermediate 10 was dissolved in acetonitrile (2ml) then treated with phosphorous oxychloride (0.101g) and stirred under nitrogen at 90°C for 3.5h. The mixture was concentrated in vacuo and the residue partitioned between DCM and saturated aqueous sodium bicarbonate solution. The organic layer was concentrated in vacuo and the residue applied to a SPE cartridge (silica, 5g), which was eluted with cyclohexane : Et_2O (1:2). Fractions containing desired material were combined and concentrated in vacuo to afford Example 3 (0.034g). LCMS showed $MH^+ = 341$; $T_{RET} = 3.39$min.

Example 4: N-Cyclopentyl-1-ethyl-5-(5-methyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



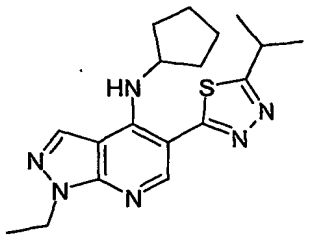
A solution of Intermediate 4 (0.09g) in acetonitrile (5ml) was stirred under nitrogen and treated with Lawesson's reagent (0.116g). The mixture was heated at 65°C for 16h, then concentrated in vacuo. The residue was applied to an SPE cartridge (silica, 5g) and eluted with a gradient of cyclohexane : Et_2O (1:2 then 1:3, 1:4, 1:5, 0:1). Fractions containing desired material were combined and concentrated in vacuo. Further purification was achieved using mass directed autoprep HPLC to afford Example 4 (0.002g). LCMS showed $MH^+ = 339$; $T_{RET} = 3.23$min.

Example 5: N-Cyclopentyl-1-ethyl-5-{5-[(methylsulfonyl)methyl]-1,3,4-thiadiazol-2-yl}-1H-pyrazolo[3,4-b]pyridin-4-amine



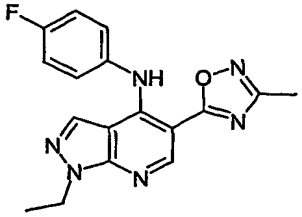
A solution of Intermediate 5 (0.07g) in acetonitrile (3ml) was stirred under nitrogen and treated with Lawesson's reagent (0.085g). The mixture was heated at 65°C for 136h, then concentrated in vacuo. The residue was partitioned between DCM and water and the organic layer concentrated in vacuo. Further purification was achieved using mass directed autoprep HPLC to afford Example 5 (0.008g). LCMS showed $MH^+ = 407$; $T_{RET} = 2.98$min.

Example 6: N-Cyclopentyl-1-ethyl-5-(5-isopropyl-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



Intermediate 10 was dissolved in acetonitrile (5ml) then treated with Lawesson's reagent (0.125g) and heated under nitrogen at 65°C for 66h. Volatiles were removed in vacuo and the residue was purified by mass directed autoprep HPLC to afford Example 6. LCMS showed $MH^+ = 357$; $T_{RET} = 3.59$min.

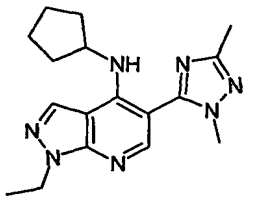
Example 7: 1-Ethyl-N-(4-fluorophenyl)-5-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



A solution of Intermediate 6 (0.04g) in ethanol (1ml) was stirred over powdered 4Å molecular sieves (0.290g) and treated with Intermediate 9 (0.045g), followed by sodium ethoxide (0.020g). The mixture was heated under reflux for 18h, then cooled and filtered. Following concentration of the filtrate in vacuo, the residue was applied to an SPE

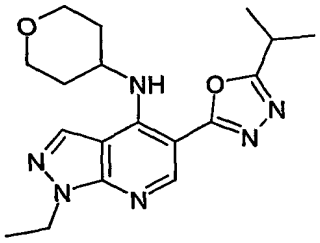
cartridge (silica, 5g) which was eluted with cyclohexane : Et_2O (1:1). Fractions containing desired material were combined and concentrated in vacuo to afford Example 7 (0.017g). LCMS showed $MH^+ = 339$; $T_{RET} = 3.23$min.

Example 8: N-Cyclopentyl-5-(1,3-dimethyl-1H-1,2,4-triazol-5-yl)-1-ethyl-1H-pyrazolo[3,4-b]pyridin-4-amine



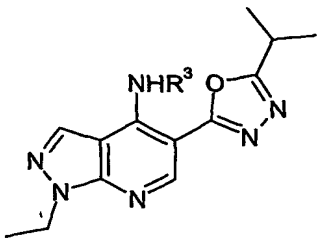
A solution of Intermediate 7 (0.06g) in ethanol (2ml) was treated with triethylamine (0.101g), followed by methyl acetimidate hydrochloride (0.033g) and the mixture heated under reflux (80°C) for 42h. Reaction was incomplete so a further portion of methyl acetimidate hydrochloride (0.033g) was added and stirring continued under reflux for 6 days. The mixture was concentrated in vacuo and the residue partitioned between DCM and 2M aqueous HCl. The organic layer was concentrated in vacuo and purified by mass directed autoprep to afford Example 8 (0.003g). LCMS showed $MH^+ = 326$; $T_{RET} = 2.66$min.

Example 9: 1-Ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



Intermediate 13 (0.016g) was dissolved in anhydrous acetonitrile (1ml). 4-Aminotetrahydropyran hydrochloride (Intermediate 21A, 0.008g) was then added, followed by diisopropylethyl amine (0.05ml) and the mixture was stirred under nitrogen at 75°C for 19h. A further portion of 4-aminotetrahydropyran (0.002g) was added and stirring continued at 85°C for 16h. The mixture was concentrated in vacuo and partitioned between DCM and water. The organic phase was concentrated in vacuo and applied to an SPE cartridge (silica, 1g), which was eluted sequentially with a gradient of EtOAc: cyclohexane (i) 1:8, (ii) 1:4, (iii) 1:2, (iv) 1:1 and (v) 1:0. Fractions containing desired material were combined and concentrated in vacuo to afford Example 9 (0.013g). LCMS showed $MH^+ = 357$; $T_{RET} = 2.89$min.

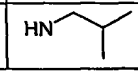
Example 10: N-cyclohexyl-1-ethyl-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



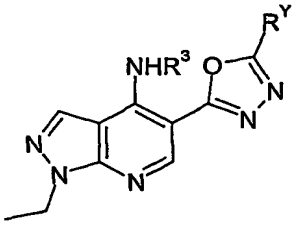
Example 10 NHR^3 = 

Intermediate 13 (0.016g, 0.055 mmol) was dissolved in anhydrous acetonitrile (1ml). Cyclohexyl amine (0.007ml, 0.061 mmol) was then added, followed by diisopropylethyl amine (0.05ml, 0.29 mmol) and the mixture was stirred under nitrogen at 75°C for 16h. The mixture was concentrated in vacuo and partitioned between DCM and water. The organic phase was concentrated in vacuo and applied to an SPE cartridge (silica, 1g), which was eluted sequentially with a gradient of EtOAc: cyclohexane (i) 1:16, (ii) 1:8, (iii) 1:4, (iv) 1:2 and (v) 1:1. Fractions containing desired material were combined and concentrated in vacuo to afford Example 10 (0.015g). LCMS showed $MH^+ = 355$; $T_{RET} = 3.59$min.

Similarly prepared using the same or similar number of moles of reagents and volumes of solvents was the following:

	NR^3R^{3a}	Starting amine	MH^+ ion	T_{RET}(min)
Example 11		Isobutyl amine	329	3.40

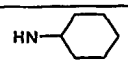
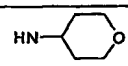
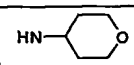
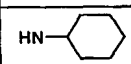
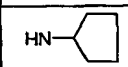
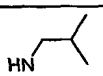
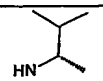
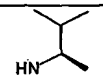
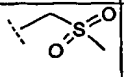
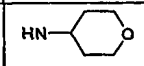
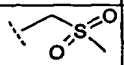
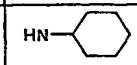
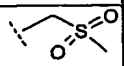
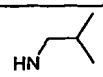
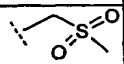
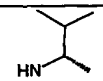
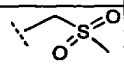
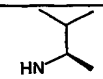
<u>Example 12:</u> 1-Ethyl-N-isobutyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



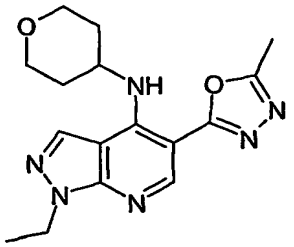
Example 12 R^Y = Me, NHR^3 = 

Intermediate 12 (0.026g, 0.1 mmol) was dissolved in ethanol (1.5ml) and treated with a solution of isobutylamine (0.007g, 0.1 mmol), also in ethanol (1ml). The mixture was then treated with diisopropylethyl amine (0.075 ml, 0.4 mmol, 4 mole equivalents) and stirred at 75°C for 16h. The mixture was concentrated in vacuo and applied to an SPE cartridge (silica, 0.5g) which was eluted sequentially with (i) chloroform, (ii) Et_2O and (iii) methanol. Fractions containing desired material were combined and concentrated in vacuo to afford Example 12 (0.024g). LCMS showed $MH^+ = 301$; $T_{RET} = 2.90$min

Similarly prepared using the same or similar number of moles of reagents and volumes of solvents were the following:

	R^Y	NR^3R^{3a}	Starting material	Amine reagent	MH^+ ion	T_{RET} (min)
Example 13	Me		Intermediate 12	Cyclohexylamine	327	3.12
Example 14	Me		Intermediate 12	4-Amino tetrahydropyran	329	2.49
Example 15	Me		Intermediate 12	(R)-(-)-3-methyl-2-butylamine	315	3.00
Example 16	Me		Intermediate 12	(S)-(-)-3-methyl-2-butylamine	315	3.00
Example 17	^{t}Bu		Intermediate 14	4-Amino tetrahydropyran	371	2.99
Example 18	^{t}Bu		Intermediate 14	Cyclohexylamine	369	3.64
Example 19	^{t}Bu		Intermediate 14	Cyclopentylamine	355	3.48
Example 20	^{t}Bu		Intermediate 14	Isobutylamine	343	3.43
Example 21	^{t}Bu		Intermediate 14	(S)-(-)-3-methyl-2-butylamine	357	3.53
Example 22	^{t}Bu		Intermediate 14	(R)-(-)-3-methyl-2-butylamine	357	3.53
Example 23			Intermediate 15	4-Amino tetrahydropyran	407	2.44
Example 24			Intermediate 15	Cyclohexylamine	405	3.00
Example 25			Intermediate 15	Isobutylamine	379	2.81
Example 26			Intermediate 15	(S)-(-)-3-methyl-2-butylamine	393	2.90
Example 27			Intermediate 15	(R)-(-)-3-methyl-2-butylamine	393	2.91

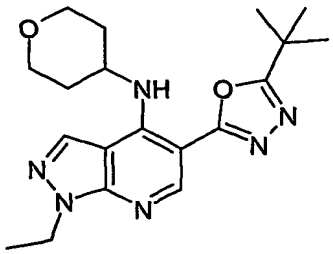
Example 14: **1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



An alternative method of preparing Example 14 is now described:

EDC (0.823g, 5.3mmol) and HOBT (0.614g, 4.55mmol) were added to Intermediate 17 (1.10g, 3.80mmol) in N,N'-dimethylformamide (10ml). The mixture was stirred for 1.5 hours then acetic hydrazide (0.421g, 5.7mmol) (commercially available e.g. from Aldrich) was added and the reaction mixture stirred at 20 °C for 48 hours. The reaction mixture was evaporated and the residue partitioned between chloroform and water. The aqueous phase was extracted with chloroform and the combined organic phases were washed with saturated aqueous sodium chloride solution then dried (Na_2SO_4) and evaporated. Phosphorus oxychloride (10ml) was added to the residue and the mixture heated at 120 °C for 0.5 hours. The reaction mixture was evaporated in vacuo and the residue applied to an SPE cartridge (silica, 20g). The cartridge was eluted with dichloromethane, cyclohexane:ethyl acetate (2:1 then 1:1), ethyl acetate, chloroform:methanol (19:1 followed by 9:1). Fractions containing the required compounds were combined and evaporated in vacuo. The residue was then chromatographed on the Biotage (silica, 50g) using cyclohexane:ethyl acetate (2:1 then 1:1), ethyl acetate followed by ethyl acetate:ethanol (19:1, 9:1 then 9:2). The residue was partitioned between dichloromethane and aqueous sodium hydrogencarbonate solution. The organic phase was dried (Na_2SO_4) and evaporated in vacuo to give Example 14 as a pale yellow solid (0.93g). LCMS showed MH^+ = 329, T_{RET} = 2.54min. ^1H NMR (400MHz in $CDCl_3$, 27°C, δppm) 9.12 (br m, 1H), 8.72 (s, 1H), 8.01 (s, 1H), 4.52 (q, 2H), 4.24 (m, 1H), 4.08 (m, 2H), 3.67 (m, 2H), 2.65 (s, 3H), 2.20 (m, 2H), 1.86 (m, 2H), 1.53 (t, 3H).

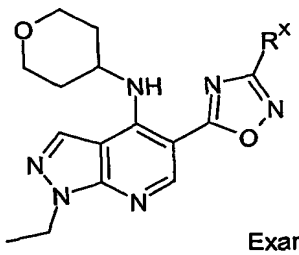
Example 17: **5-[5-(1,1-Dimethylethyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



An alternative method of preparing Example 17 is now described:

EDC (1.30g, 6.76mmol) and HOBT (0.782g, 5.80mmol) were added to Intermediate 17 (1.40g, 4.83mmol) in N,N'-dimethylformamide (20ml). The mixture was stirred for 0.5 hours then pivalic acid hydrazide (0.616g, 5.3mmol) (commercially available from Fluorochem Ltd, Wesley Stree, Glossop, Derbyshire SK13 9RY, United Kingdom or can be prepared according to the procedure by K. Ohmoto et al. in *J. Med. Chem.*, 2001, 44(8), 1268) was added and the reaction mixture stirred at 20 °C for 18 hours. The reaction mixture was evaporated and the residue partitioned between dichloromethane and water. The organic phase was washed with water, saturated aqueous sodium hydrogen carbonate solution followed by saturated aqueous sodium chloride solution then evaporated in vacuo. Phosphorus oxychloride (10ml) was added to the residue and the mixture heated at 120 °C for 3 hours. The reaction mixture was evaporated in vacuo and the residue partitioned between dichloromethane and water. The organic phase was washed with aqueous sodium hydrogen carbonate solution then dried and evaporated in vacuo. The residue was applied to an SPE cartridge and eluted with cyclohexane: ethyl acetate (3:1 followed by 7:3). The solvent was evaporated in vacuo to give Example 17 as a white solid (0.65g). LCMS showed MH^+ = 371, T_{RET} = 3.05min. ^1H NMR (400MHz in $CDCl_3$, 27°C, δppm) 9.18 (br m, 1H), 8.75 (s, 1H), 8.01 (s, 1H), 4.52 (q, 2H), 4.25 (m, 1H), 4.08 (m, 2H), 3.67 (m, 2H), 2.20 (m, 2H), 1.84 (m, 2H), 1.57-1.49 (m, 12H).

Example 28: 1-Ethyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



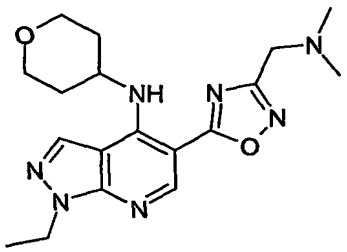
Example 28 R^X = Me

A solution of Intermediate 16 (0.05g, 0.157 mmol) in ethanol (2ml) was stirred over powdered 4Å molecular sieves (0.30g) and treated with a solution of Intermediate 9 (0.059g, 0.8 mmol) and sodium ethoxide (0.027g, 0.4 mmol) in ethanol (1ml). The mixture was heated at reflux for 18h under nitrogen, then cooled and filtered. Following concentration of the filtrate in vacuo, the residue was applied to an SPE cartridge (silica, 5g) which was eluted with cyclohexane : EtOAc (1:1). Fractions containing desired material were combined and concentrated in vacuo to afford Example 28 (0.024g). LCMS showed MH^+ = 329; T_{RET} = 2.86 min.

Similarly prepared using the same or similar number of moles of reagents and volumes of solvents were the following:

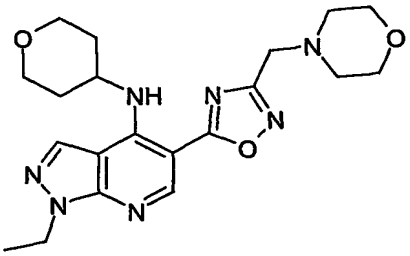
	R^X	Starting Amidoxime	MH^+ ion	T_{RET} (min)
Example 29	CH_2OMe	Intermediate 22	359	2.78

Example 30: 5-{3-[(Dimethylamino)methyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



A solution of Intermediate 16 (0.05g) in ethanol (2ml) was stirred over powdered 4Å molecular sieves (0.30g) and treated with a solution of Intermediate 23 (0.094g) and sodium ethoxide (0.027g) in ethanol (1ml). The mixture was heated at reflux for 18h under nitrogen, then cooled and filtered. Following concentration of the filtrate in vacuo, the residue was applied to an SPE cartridge (silica, 5g) which was eluted with 2-5% methanol in DCM. Fractions containing desired material were combined and concentrated in vacuo, then applied to a further SPE cartridge (aminopropyl, 1g) which was eluted with methanol to afford Example 30 (0.02g). LCMS showed $MH^+ = 372$; $T_{RET} = 2.10$ min.

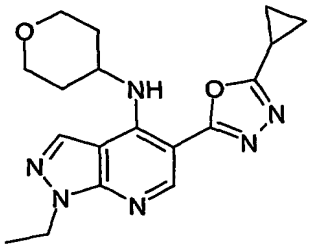
Example 31: 1-Ethyl-5-[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



A solution of Intermediate 16 (0.05g) in ethanol (2ml) was stirred over powdered 4Å molecular sieves (0.30g) and treated with a solution of Intermediate 24 (0.128g) and sodium ethoxide (0.027g) in ethanol (1ml). The mixture was heated at reflux for 18h under nitrogen, then cooled and filtered. Following concentration of the filtrate in vacuo, the residue was applied to an SPE cartridge (silica, 5g) which was eluted with 2-5% methanol in DCM. Fractions containing desired material were combined and

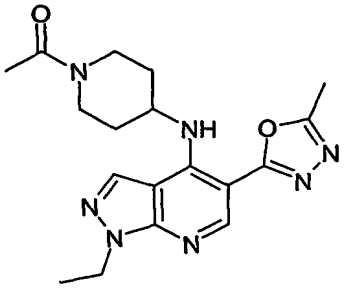
concentrated in vacuo to afford Example 31 (0.025g). LCMS showed $MH^+ = 415$; $T_{RET} = 2.46$ min.

Example 32: 5-(5-Cyclopropyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



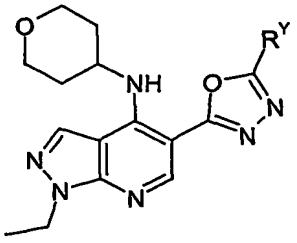
A solution of Intermediate 20 (0.020g) in THF (0.2ml) was treated with Burgess reagent (0.026g) and heated in a microwave at 120°C (100W) for 5min. The mixture was concentrated by evaporation under a stream of nitrogen and the residue applied to an SPE cartridge (silica, 1g) which was eluted with 2% methanol in DCM to afford Example 32 as a white solid (0.014g). LCMS showed $MH^+ = 355$; $T_{RET} = 2.78$ min.

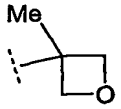
Example 33: N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



Intermediate 12 (0.03g) was dissolved in acetonitrile (2ml) and treated with DIPEA (0.1ml) and Intermediate 25 (0.022g). The mixture was stirred at 85°C for 18h then concentrated in vacuo and partitioned between DCM and water. The layers were separated and the organic layer concentrated in vacuo, then purified by mass directed autoprep HPLC to afford Example 33 (0.01g). LCMS showed $MH^+ = 370$; $T_{RET} = 2.48$min.

Example 34: 1-Ethyl-5-[5-(3-methyloxetan-3-yl)-1,3,4-oxadiazol-2-yl]-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine



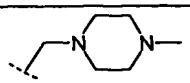
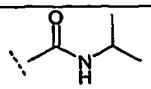
Example 34 R^Y = 

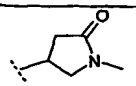
A solution of Intermediate 19 (0.05g, 0.133 mmol), TBTU (0.045g, 0.14 mmol) and DIPEA (0.1ml, ca. 0.5 mmol) in DMF (1ml) is stirred at room temperature under nitrogen for 5 min. A solution of Intermediate 26 (0.024g, 0.21 mmol) in DMF (1ml) is then added and stirring continued for 18h. Reaction can be found to be incomplete after this time so a further portion of Intermediate 26 (0.012g, 0.10 mmol) is added and stirring continued under nitrogen for a further 18h. The mixture is concentrated in vacuo then the residue applied to an SPE cartridge (aminopropyl, 2g), which is eluted with methanol (2x3ml). Fractions containing desired material are concentrated in vacuo.

The partially purified intermediate is taken forward without further characterisation and si dissolved in THF (0.5ml) then treated with Burgess reagent (0.025g, ca. 0.1 mmol). The mixture is heated under microwave conditions at 120°C (120W) for 5 min. The mixture is then concentrated in vacuo and purified by mass directed autoprep HPLC to afford Example 34.

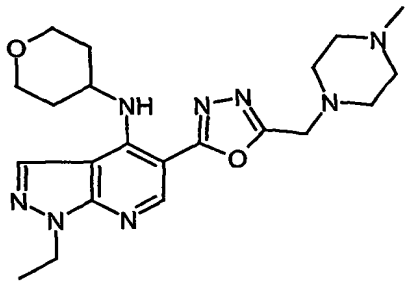
According to an alternative and more preferred embodiment, the reaction was performed as follows. A solution of carboxylic acid Intermediate 26 (0.024g, 0.21 mmol), TBTU (0.045g, 0.14 mmol) and DIPEA (0.1ml, ca. 0.5 mmol) in DMF (1ml) was stirred at room temperature under nitrogen for 5 min. A solution of Intermediate 19 (0.05g, 0.133 mmol) in DMF (1ml) was then added and stirring continued for 18h. Reaction was found to be incomplete after this time so a further portion of Intermediate 26 (0.012g, 0.10 mmol) was added and stirring continued under nitrogen for a further 18h. The mixture was concentrated in vacuo then the residue applied to an SPE cartridge (aminopropyl, 2g), which was eluted with methanol (2x3ml). Fractions containing desired material were concentrated in vacuo. The partially purified intermediate was taken forward without further characterisation and was dissolved in THF (0.5ml) then treated with Burgess reagent (0.025g, ca. 0.1 mmol). The mixture was heated under microwave conditions at 120°C (120W) for 5 min. The mixture was then concentrated in vacuo and purified by mass directed autoprep HPLC to afford Example 34 (0.006g). LCMS showed MH^+ = 385; T_{RET} = 2.65min.

Similarly prepared, via the original or alternative embodiment described above, and using the same or similar number of moles of reagents and volumes of solvents, were the following:

	R^Y	Starting Carboxylic Acid (instead of Intermediate 26)	MH^+ ion	T_{RET} (min)
Example 35		Intermediate 27	427	2.14
Example 36		Intermediate 28	400	2.87

Example 37		Intermediate 29	412	2.39

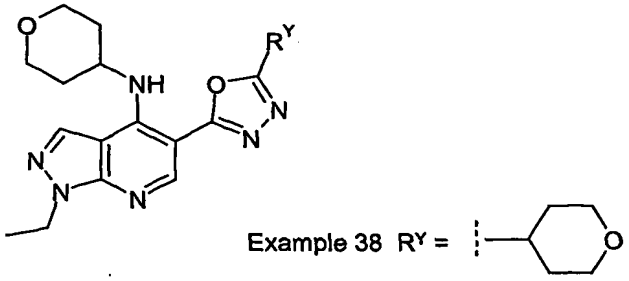
Example 35: 1-Ethyl-5-{5-[(4-methyl-1-piperazinyl)methyl]-1,3,4-oxadiazol-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine



An alternative method of preparing Example 35 is now described:

A solution of Intermediate 27 (0.463g, 2.93mmol), TBTU (0.941g, 2.93mmol) and DIPEA (1.53ml, 8.79mmol) in dry dimethylformamide (7ml) was stirred at room temperature for 15min. A solution of Intermediate 19 (1.0g, 2.93mmol) in dry dimethylformamide (5ml) was then added and stirring was continued for 1h. The mixture was concentrated in vacuo, and the residue was dissolved in methanol (5ml) and applied equally to two SPE cartridges (aminopropyl, 10g). The cartridges were eluted with methanol. The product-containing fractions were combined and evaporated to give a yellow oil (1.56g) which was dissolved in dichloromethane (10ml) and applied to a SPE cartridge (silica, 10g). The cartridge was eluted with chloroform-methanol-triethylamine (9/0.2/0.1). Fractions containing the desired product were combined and evaporated to give a pale yellow foam (1.17g). This product was suspended in dry tetrahydrofuran (45ml) and treated with Burgess reagent (1.244g, 5.22mmol) at room temperature under nitrogen. The resulting solution was heated at 70°C. After 2h, the reaction mixture was evaporated and the residual oil was dissolved in dichloromethane (5ml) and applied to a SPE cartridge (silica, 20g). The cartridge was eluted with chloroform-methanol-triethylamine (9/0.2/0.1). Fractions containing the desired material were combined and evaporated to give a cream solid. Further purification by passage through a SCX cartridge (20g) eluting with methanol followed by 10% ammonia in methanol afforded Example 35 as a buff coloured solid (0.72g). LCMS showed $MH^+ = 427$, $T_{RET} = 2.02$min. ^{1}H NMR (400MHz in $CDCl_3$, 27°C, δppm) 9.11 (d, 7Hz, 1H), 8.76 (s, 1H), 8.01 (s, 1H), 4.52 (q, 2H), 4.24 (m, 1H), 4.08 (m, 2H), 3.93 (s, 2H) 3.66 (m, 2H), 2.8 - 2.5 (br m's, 4H), 2.31 (s, 3H), 2.20 (m, 2H), 1.85 (m, 2H), 1.52 (t, 3H).

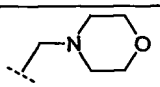
Example 38: 1-Ethyl-N-(tetrahydro-2H-pyran-4-yl)-5-[5-(tetrahydro-2H-pyran-4-yl)-1,3,4-oxadiazol-2-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine



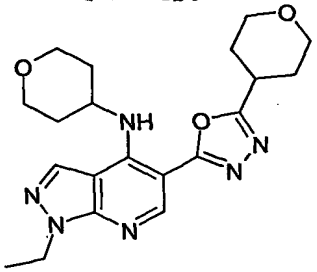
A solution of Intermediate 19 (0.05g, 0.133 mmol), TBTU (0.045g, 0.14 mmol) and DIPEA (0.1ml, ca. 0.5 mmol) in DMF (1ml) is stirred at room temperature under nitrogen for 5 min. A solution of Intermediate 30 (0.018g, 0.14 mmol) in DMF (1ml) is then added and stirring continued for 18h. Reaction can be found to be incomplete after this time so a further portion of Intermediate 30 (0.009g, 0.07 mmol) is added and stirring continued under nitrogen for a further 18h. The mixture is concentrated in vacuo then the residue applied to an SPE cartridge (aminopropyl, 2g), which is eluted with methanol (2x3ml). Fractions containing desired material are concentrated in vacuo. The partially purified intermediate is taken forward without further characterisation and is dissolved in THF (0.5ml) then treated with Burgess reagent (0.025g, ca. 0.1 mmol). The mixture is heated under microwave conditions at 120°C (120W) for 5 min. Reaction can appear incomplete so a further portion of Burgess Reagent (0.012g, ca. 0.05 mmol) is added and the mixture heated under microwave conditions at 140°C (120W) for a further 10 min. The mixture is then concentrated in vacuo and purified by mass directed autoprep HPLC to afford Example 38.

According to an alternative and more preferred embodiment, the reaction was performed as follows. A solution of carboxylic acid Intermediate 30 (0.018g, 0.14 mmol), TBTU (0.045g, 0.14 mmol) and DIPEA (0.1ml, ca. 0.5 mmol) in DMF (1ml) was stirred at room temperature under nitrogen for 5 min. A solution of Intermediate 19 (0.05g, 0.133 mmol) in DMF (1ml) was then added and stirring continued for 18h. Reaction was found to be incomplete after this time so a further portion of Intermediate 30 (0.009g, 0.07 mmol) was added and stirring continued under nitrogen for a further 18h. The mixture was concentrated in vacuo then the residue applied to an SPE cartridge (aminopropyl, 2g), which was eluted with methanol (2x3ml). Fractions containing desired material were concentrated in vacuo. The partially purified intermediate was taken forward without further characterisation and was dissolved in THF (0.5ml) then treated with Burgess reagent (0.025g, ca. 0.1 mmol). The mixture was heated under microwave conditions at 120°C (120W) for 5 min. Reaction appeared incomplete so a further portion of Burgess Reagent (0.012g, ca. 0.05 mmol) is added and the mixture heated under microwave conditions at 140°C (120W) for a further 10 min. The mixture was then concentrated in vacuo and purified by mass directed autoprep HPLC to afford Example 38 (0.006g). LCMS showed $MH^+ = 399$; $T_{RET} = 2.64$min.

Similarly prepared, via the original or alternative embodiment described above, and using the same or similar number of moles of reagents and volumes of solvents, were the following:

	R^Y	Starting Carboxylic Acid (instead of Intermediate 30)	MH^+ ion	T_{RET} (min)
Example 39		Intermediate 31	414	2.44
Example 40	CH_2O^tBu	Intermediate 32	401	2.98

Example 38: 1-Ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-5-[5-(tetrahydro-2*H*-pyran-4-yl)-1,3,4-oxadiazol-2-yl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine

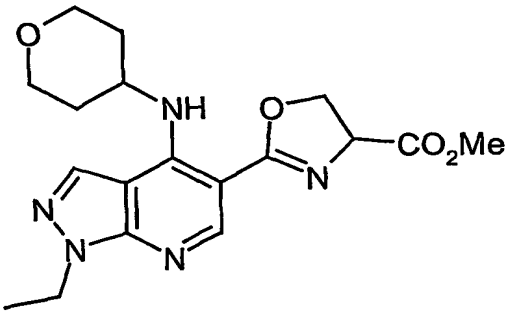


An alternative method of preparing Example 38 is now described:

A mixture of Intermediate 30 (0.325g, 2.5mmol), TBTU (0.803g, 2.5mmol) and DIPEA (1.75ml, 10.04mmol) in N,N-dimethylformamide (10ml) was stirred at 20 °C for 20 minutes. A suspension of Intermediate 19 (1.024g, 3.00mmol) in N,N-dimethylformamide was added and the reaction mixture stirred for 18 hours. The solvent was evaporated and the residue applied to SPE cartridges (2 x 50g, aminopropyl). The cartridges were eluted with dichloromethane:methanol (0 - 100% methanol over 17 minutes at 25ml/min). Appropriate fractions were evaporated in vacuo and the residue dissolved in tetrahydrofuran (10ml). Burgess Reagent (0.746g, 3.13mmol) was added and the reaction mixture was heated at reflux for 2.5 hours. Additional Burgess Reagent (0.284g) was added and heating continued for 1.5 hours. The solvent was evaporated in vacuo. The residue was applied to an SPE cartridge (silica, 100g) and eluted with cyclohexane:ethyl acteate (gradient of 0 to 100% ethyl acetate over 25 minutes at 25ml/min) followed by ethyl acetate then ethyl acetate:methanol (4:1). Appropriate fractions were combined and evaporated to give Example 38 as a white solid (0.503g). LCMS showed $MH^+ = 399$, $T_{RET} = 2.67$min. ^1H NMR (400MHz in $CDCl_3$, 27°C, δppm)

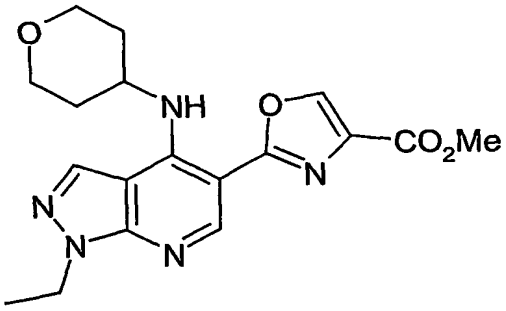
9.14 (br m, 1H), 8.72 (s, 1H), 8.01 (s, 1H), 4.52 (q, 2H), 4.24 (m, 2H), 4.10 (m, 4H), 3.64 (m, 4H), 3.27 (m, 1H), 2.25-1.96 (m, 6H), 1.85 (m, 2H), 1.53 (t, 3H).

Example 40A: Methyl 2-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-4,5-dihydro-1,3-oxazole-4-carboxylate

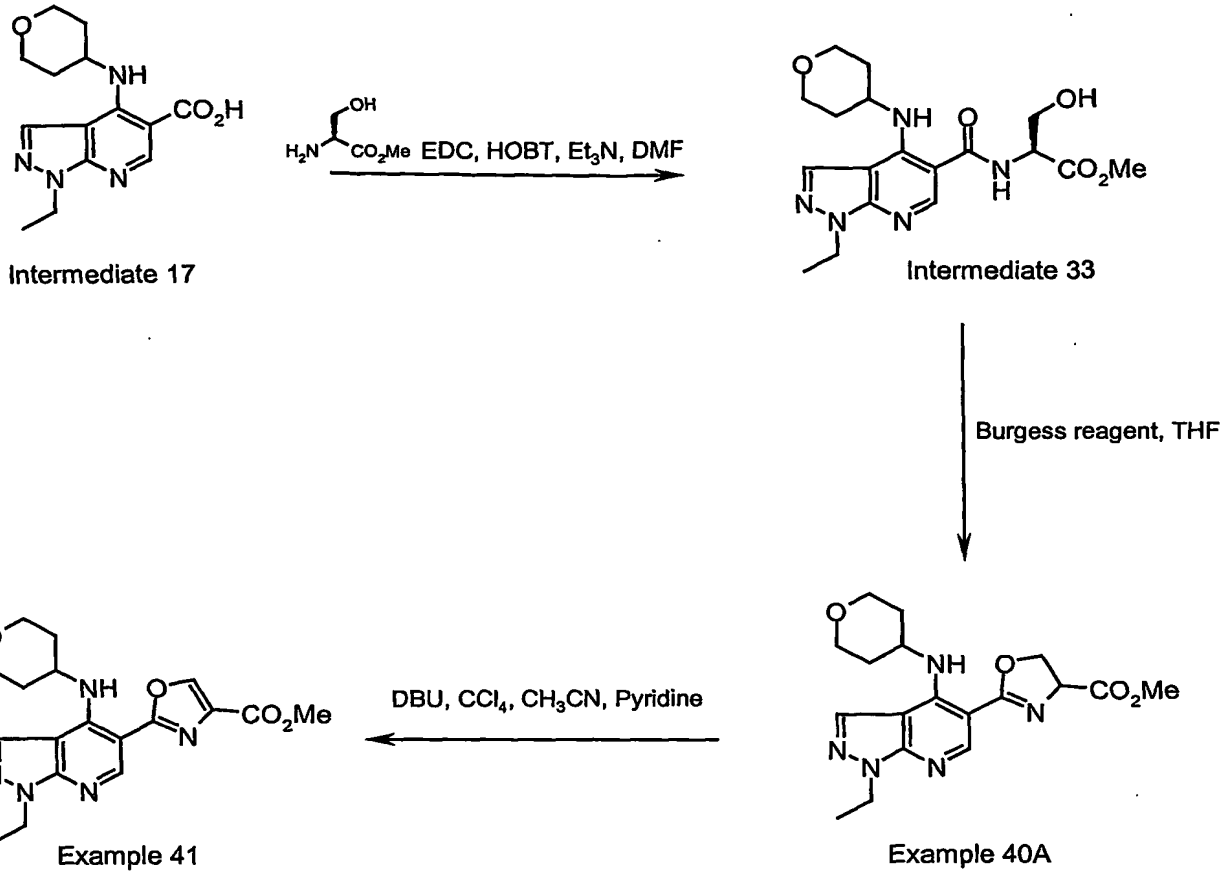


Intermediate 33 (0.055g, 0.14mmol) and Burgess reagent (0.037g, 0.16mmol) were suspended in THF (2ml) and heated at reflux for 4 hours. Solvents were removed in vacuo and the residue applied to an SPE cartridge (silica, 2g), which was eluted with cyclohexane:ethyl acetate (1:2). Concentration in vacuo afforded Example 40A (0.03g). LCMS showed $MH^+ = 374$, $T_{RET} = 2.78$min.

Example 41: Methyl 2-[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3-oxazole-4-carboxylate



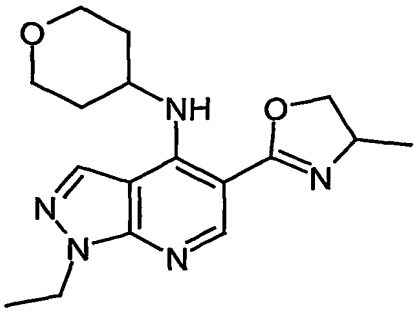
The compound of Example 41 was synthesised using the following route, reagents and solvents:



In one embodiment, a suitable detailed procedure for the first two steps is given above in "Intermediate 33" and "Example 40A". In one embodiment, a suitable detailed procedure for synthesising Example 41 from Example 40A is as follows:

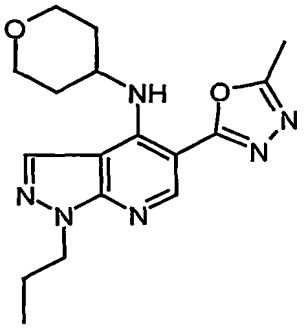
Example 40A (0.023g, 0.062mmol) and DBU (0.028g, 0.18mmol) were dissolved in carbon tetrachloride/acetonitrile/pyridine (2:3:3, 1.6ml) and stirred at room temperature under nitrogen for 48 hours. Solvents were removed in vacuo and the residue was purified by mass directed autoprep HPLC to afford Example 41 (0.0017g). LCMS showed $MH^+ = 372$, $T_{RET} = 9.24$min.

Example 42: 1-Ethyl-5-(4-methyl-4,5-dihydro-1,3-oxazol-2-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine

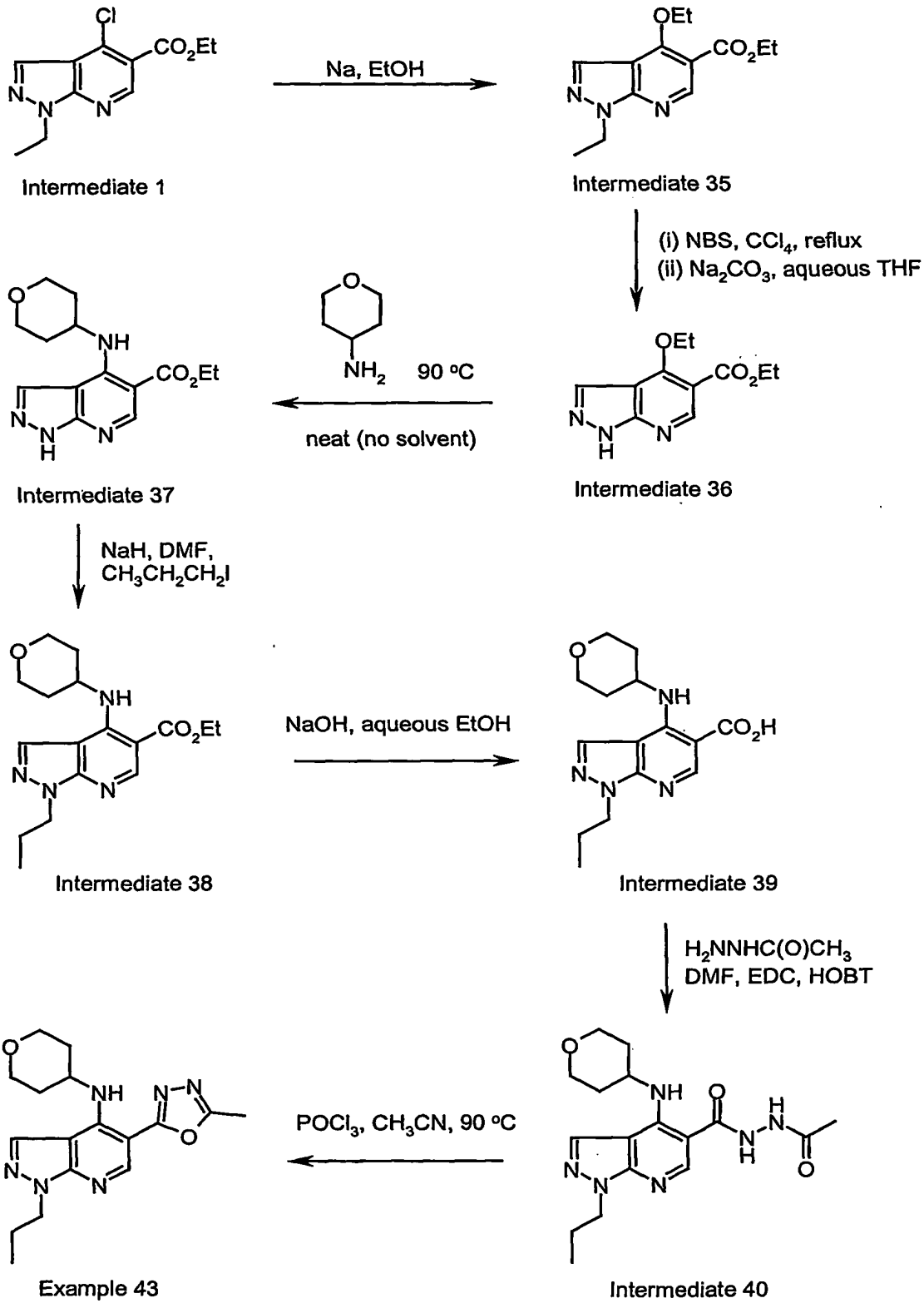


Intermediate 34 (0.095g, 0.27mmol) and Burgess reagent (0.071g, 0.30mmol) were dissolved in THF (2ml) and heated at reflux for 4 hours. Solvents were removed in vacuo and the residue applied to an SPE (silica, 5g), which was eluted with ethyl acetate to afford Example 42 (0.045g). LCMS showed $MH^+ = 330$, $T_{RET} = 2.84$min.

Example 43: 1-n-Propyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



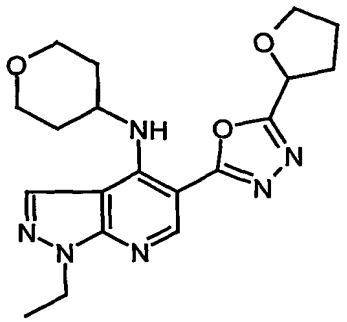
Example 43 was synthesised according to the following reaction scheme:



Detailed conditions which can be used for the first six reactions from Intermediate 1 to Intermediate 40 are given in the "Intermediate" syntheses hereinabove for Intermediates 35, 36, 37, 38, 39 and 40.

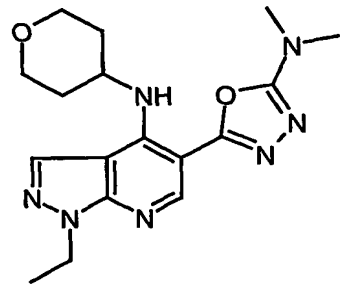
Example 43 can be made from Intermediate 40 using a similar process to that described for Example 1, 2, 3, using a similar or the same number of moles of reagents and/or volumes of solvents. LCMS showed $MH^+ = 343$, $T_{RET} = 2.70$min.

Example 44: 1-Ethyl-5-[5-(tetrahydrofuran-2-yl)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



A solution of Tetrahydro-2-furoic acid = 2-(tetrahydrofuran)carboxylic acid (commercially available from Sigma-Aldrich) (0.012ml, 0.12mmol), TBTU (0.039g, 0.12mmol) and DIPEA (0.084ml, 0.48mmol) in DMF (2ml) was stirred at room temperature under nitrogen. Intermediate 19 (0.045g, 0.12mmol) was added and the reaction stirred for 2 days. The mixture was concentrated in vacuo then the residue applied to an SPE cartridge (aminopropyl, 5g), which was eluted with methanol. Fractions containing the desired material were concentrated in vacuo. Half of the partially purified material was dissolved in THF (0.1ml) and treated with Burgess reagent (0.015g, 0.06mmol). The mixture was heated under microwave conditions at 120 °C (100W) for 5 minutes. The mixture was then concentrated in vacuo and applied to an SPE cartridge (silica, 0.5g). The cartridge was eluted with dichloromethane: methanol (19:1), fractions containing the desired material were concentrated in vacuo. The sample was then partitioned between dichloromethane and water, the organic phase was evaporated to give Example 44 (0.0065g). LCMS showed $MH^+ = 385$, $T_{RET} = 2.69$min.

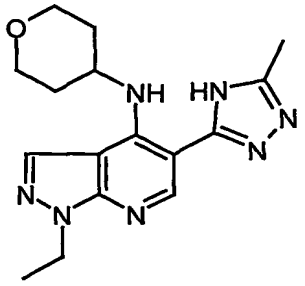
Example 45: 1-Ethyl-5-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



Intermediate 86 (0.113g, 0.28mmol) and Burgess Reagent (0.133g, 0.56mmol) in THF (1ml) were heated in the microwave 5 minutes at 120 °C SmithCreator Microwave. The

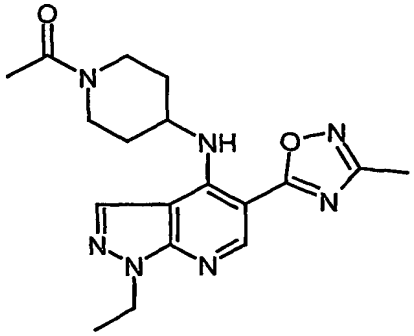
sample was evaporated in vacuo and the residue purified by mass directed autoprep HPLC...LCMS showed $MH^+ = 358$; $T_{RET} = 2.57$min

Example 46: 1-Ethyl-5-(5-methyl-1,2,4-triazol-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



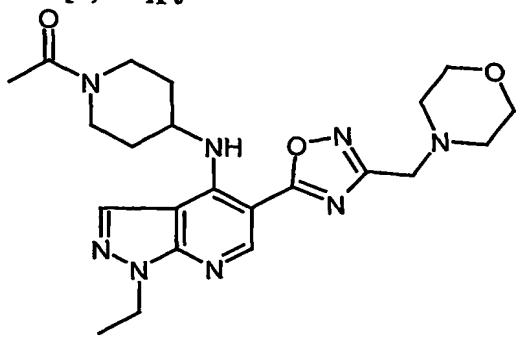
A solution of the Intermediate 19 (0.1g, 0.29mmol), diisopropylethylamine (0.3ml, 1.74mmol) and methyl acetimidate hydrochloride (0.095g, 0.87mmol, commercially available from Aldrich) in ethanol (3ml) was heated under reflux. After 17h, the reaction mixture was evaporated to an oily residue which was partitioned between dichloromethane (10ml) and water (2ml). The phases were separated and the organic phase was dried over anhydrous sodium sulphate and evaporated to a waxy solid (0.053g). Purification of a portion of this solid (0.025g) by mass directed autoprep HPLC afforded Example 46 (0.005g). LCMS showed $MH^+ = 328$; $T_{RET} = 2.25$min.

Example 47: N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



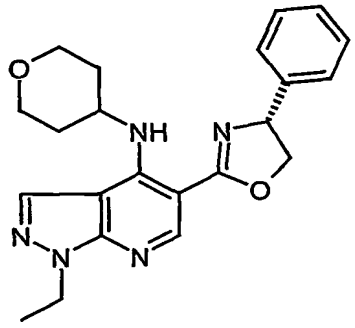
A mixture of Intermediate 41 (0.049mg, 0.14mmol), Intermediate 9 (0.051g, 0.68mmol), sodium ethoxide (0.13ml, 21% solution in ethanol, commercially available from Aldrich) and powdered 4Å molecular sieves (0.3g) in ethanol (2ml) were heated at 80 °C for 16 hours under nitrogen. The mixture was cooled and filtered and the filtrate concentrated in vacuo. The residue was applied to an SPE cartridge (silica, 5g) and eluted with cyclohexane, cyclohexane:ethyl acetate (1:1) and then ethyl acetate. The desired fractions were combined and evaporated to give Example 47 (0.005g). LCMS showed $MH^+ = 370$; $T_{RET} = 2.77$min

Example 48: N-(1-Acetylpiperidin-4-yl)-1-ethyl-5-[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine



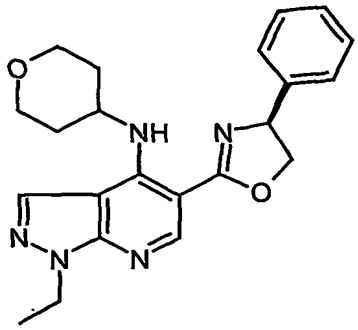
Example 48 was prepared from Intermediate 41 and Intermediate 24 using an analogous method to that for Example 47. LCMS showed $MH^+ = 455$; $T_{RET} = 2.59$min.

Example 49 **1-Ethyl-5-[(4*R*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



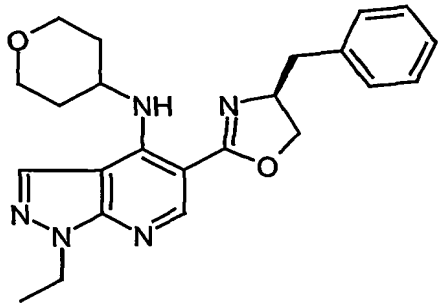
Burgess reagent (0.189g, 0.79mmol) was added portionwise, over 3min, to a stirred solution of Intermediate 42 (0.293g, 0.72mmol) in dry tetrahydrofuran (13ml) at room temperature under nitrogen. The resulting solution was heated at 70°C under nitrogen for 4h. The reaction mixture was evaporated to give an off-white solid which was dissolved in dichloromethane (5ml) and applied to a SPE cartridge (silica, 10g). The cartridge was eluted sequentially with a gradient of ethyl acetate-petroleum ether (1:8, 1:4, 1:2, 1:1, 1:0). Fractions containing the desired product were combined and evaporated to afford Example 49 as a white crystalline solid (0.169g). LCMS showed $MH^+ = 392$; $T_{RET} = 3.31$min.

Example 50 **1-Ethyl-5-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



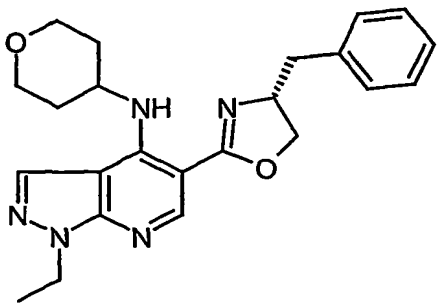
Example 50 was prepared from Intermediate 43 using an analogous method to that for Example 49. LCMS showed $MH^+ = 392$; $T_{RET} = 3.32$min.

Example 51 **1-Ethyl-5-[(4*S*)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



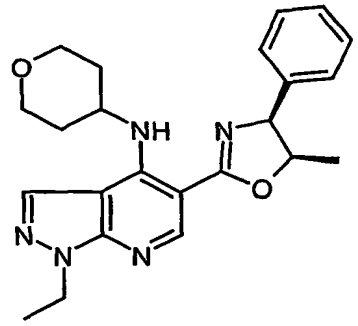
Example 51 was prepared from Intermediate 44 using an analogous method to that for Example 49. LCMS showed $MH^+ = 406$; $T_{RET} = 3.38$min.

Example 52 **1-Ethyl-5-[(4*R*)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



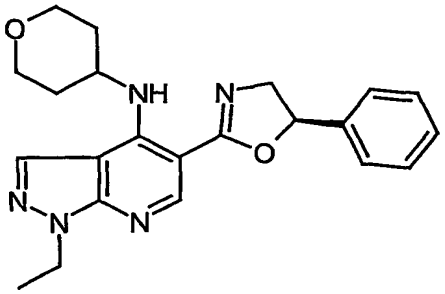
Example 52 was prepared from Intermediate 45 using an analogous method to that for Example 49. LCMS showed $MH^+ = 406$; $T_{RET} = 3.38$min.

Example 53 **1-Ethyl-5-[(4*S*,5*R*)-5-methyl-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



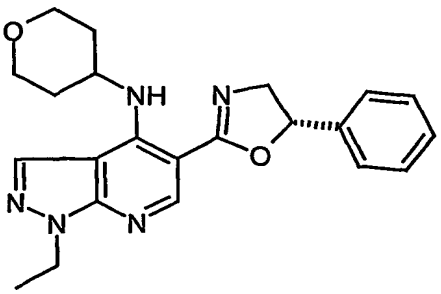
Example 53 was prepared from Intermediate 46 using an analogous method to that for Example 49. LCMS showed $MH^+ = 406$; $T_{RET} = 3.37$min.

Example 54 **1-Ethyl-5-[(5*R*)-5-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



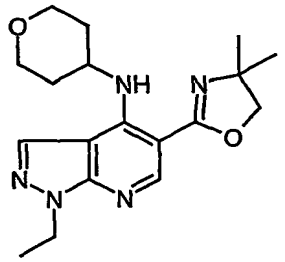
Example 54 was prepared from Intermediate 47 using an analogous method to that for Example 49. LCMS showed $MH^+ = 392$; $T_{RET} = 3.29$min.

Example 55 **1-Ethyl-5-[(5*S*)-5-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



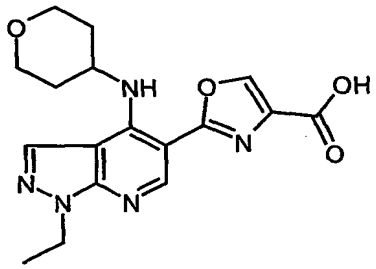
Example 55 was prepared from Intermediate 48 using an analogous method to that for Example 49. LCMS showed $MH^+ = 392$; $T_{RET} = 3.29$min.

Example 56 **5-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



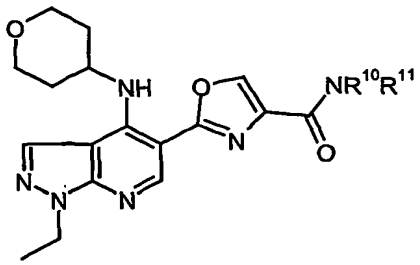
Example 56 was prepared from Intermediate 49 using an analogous method to that for Example 49. LCMS showed $MH^+ = 344$; $T_{RET} = 2.95$min.

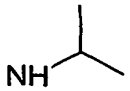
Example 57: 2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1,3-oxazole-4-carboxylic acid



A solution of lithium hydroxide (0.12g, 5.2mmol) in water (6ml) was added to a suspension of Example 41 (0.48g, 1.3mmol) in methanol (20ml) and the resultant mixture heated at 50 °C for 2 hours. The solvent was evaporated in vacuo and the residue dissolved in water (50ml), cooled in an ice bath and acidified to pH 3 by the addition of aqueous hydrochloric acid. The precipitate was filtered, washed with water and dried in vacuo at 40 °C to give Example 57 as a white solid (0.3g). LCMS showed $MH^+ = 358$; $T_{RET} = 2.62$min

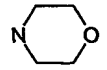
Example 58: 2-[1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-5-yl]-N-(1-methylethyl)-1,3-oxazole-4-carboxamide



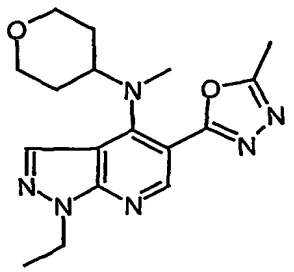
Example 58, $NR^{10}R^{11}$ = 

A mixture of Example 57 (0.05g, 0.14mmol), HOBT (0.023g, 0.17mmol), EDC (0.038g, 0.2mmol) in DMF (2ml) were stirred at 20 °C for 20 minutes. Isopropylamine (0.013ml, 0.15mmol) was added and the reaction mixture stirred overnight. The solvent was concentrated in vacuo and the residue dissolved in DCM. The organic phase was washed with water then aqueous sodium hydrogen carbonate solution. The aqueous phases were extracted with DCM and the combined organic phases concentrated in vacuo. The residue was applied to an SPE cartridge (aminopropyl, 2g) and eluted with MeOH, appropriate fractions were combined and evaporated in vacuo. The residue was further purified by chromatography on SPE (silica, 0.5g) eluting with cyclohexane:ethyl acetate (2:1 followed by 1:1) to give Example 58 as a white solid (0.012g). LCMS showed MH^+ = 399; T_{RET} = 2.78min

Similarly prepared using the same or similar numbers of moles of reagents and/or volumes of solvents was the following:

	$NR^{10}R^{11}$	Starting amine	MH^+	T_{RET} (min)
Example 59		Morpholine	426	2.56

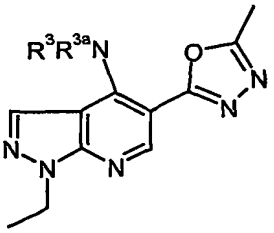
Example 60: 1-Ethyl-N-methyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine

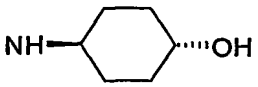


Intermediate 53 (0.076g, 0.21mmol) in phosphorous oxychloride (3ml) was heated at 120 °C for 3 hours then evaporated in vacuo. The residue was partitioned between DCM and

water and the organic phase concentrated in vacuo. The residue was purified by mass directed autoprep HPLC to afford Example 60 (0.027g). LCMS showed $MH^+ = 343$; $T_{RET} = 2.34$min

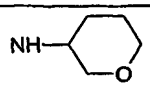
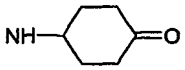
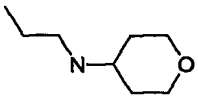
Example 61: *trans*-4-{[1-Ethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl]amino}cyclohexanol



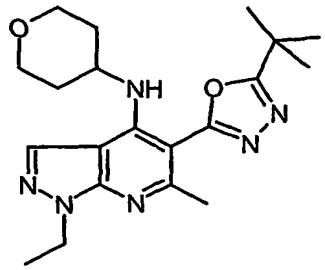
Example 61, NR^3R^{3a} = 

Intermediate 54 (0.072g, 0.63mmol), Intermediate 12 (0.150g, 0.57mmol) and diisopropylethylamine (0.51ml) in acetonitrile (3ml) were heated at 85 °C for 18 hours then evaporated in vacuo. The residue was partitioned between DCM and water and the organic phase concentrated in vacuo. The residue was purified by mass directed autoprep HPLC to afford Example 61 (0.004g). LCMS showed $MH^+ = 343$; $T_{RET} = 2.48$min

Similarly prepared using the same or similar numbers of moles of reagents and/or volumes of solvents were the following:

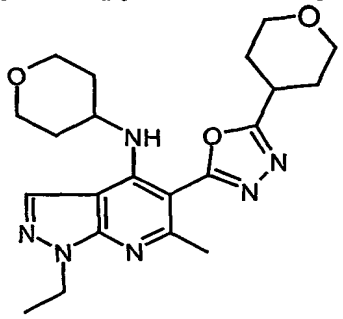
	NR^3R^{3a}	Amine $R^3R^{3a}NH$ (instead of Intermediate 54)	MH^+	T_{RET} (min)
Example 62		Intermediate 55	329	2.59
Example 63		Intermediate 56	341	2.53
Example 64		Intermediate 57	371	2.60

Example 65: 5-[5-(1,1-Dimethylethyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-6-methyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



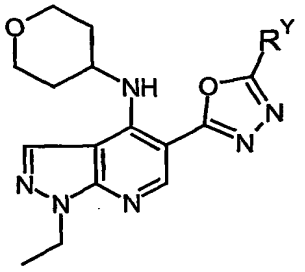
Intermediate 61 (0.266g, 0.56mmol) in phosphorous oxychloride (10ml) was heated at 120 °C for 1.5 hours then evaporated in vacuo. The residue was partitioned between DCM and water and the organic phase concentrated in vacuo. The residue was purified on an SPE cartridge (silica, 5g) eluting with cyclohexane: ethyl acetate (2:1, 1:1 then 2:3) to afford Example 65 (0.042g). LCMS showed $MH^+ = 385$; $T_{RET} = 3.05$min.

Example 66: 1-Ethyl-6-methyl-N-(tetrahydro-2H-pyran-4-yl)-5-[5-(tetrahydro-2H-pyran-4-yl)-1,3,4-oxadiazol-2-yl]-1H-pyrazolo[3,4-b]pyridin-4-amine



Intermediate 64 (0.05g, 0.11mol) and Burgess Reagent (0.053g, 0.22mol) in a mixture of THF / DMF (1ml, 1:1) were heated under microwave conditions at 120 °C (120W) for 5 minutes. The reaction mixtures were heated at 150 °C for four 10 minutes intervals with an additional portion of Burgess reagent (0.025g) being added after the first and third period of additional microwave heating. The reaction mixture was concentrated in vacuo and purified by SPE (silica, 0.5g) eluting with cyclohexane, cyclohexane: ethyl acetate (2:3 then 1:4) then ethyl acetate. Fractions containing the desired material were evaporated in vacuo to afford Example 66 (0.010g). LCMS showed $MH^+ = 413$; $T_{RET} = 2.63$min.

Example 67: 5-(5-Cyclobutyl-1,3,4-oxadiazol-2-yl)-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine

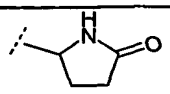
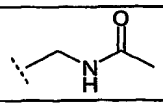
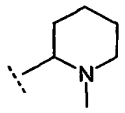
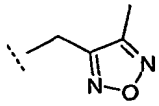
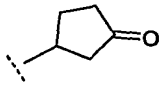
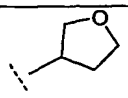
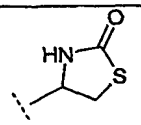
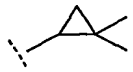
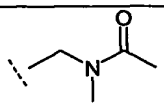
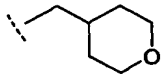
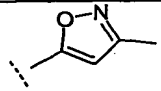
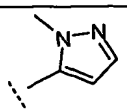


Example 67, R^Y = 

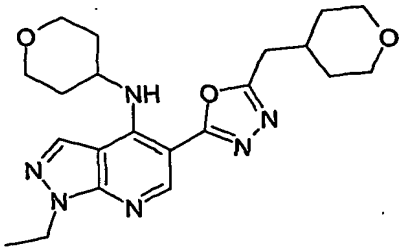
Intermediate 65 (0.05g, 0.13mmol) and Burgess Reagent (0.07g, 0.3mmol) in THF (2ml) was heated at 80 °C for 7 hours. The reaction mixture was concentrated in vacuo and a further portion of Burgess Reagent (0.07g, 0.3mmol) in THF (0.5ml) was added and the reaction mixture refluxed for 18 hours. The reaction was concentrated in vacuo and partitioned between DCM and water. The phases were separated using a hydrophobic frit (Whatman PTFE Filter Media with Polypropylene Housing 5µM pore size). The organic

phase was concentrated in vacuo and the residue purified by mass directed autoprep HPLC to afford Example 67 (0.018g). LCMS showed $MH^+ = 369$; $T_{RET} = 3.03$min.

Similarly prepared using the same or similar numbers of moles of reagents and/or volumes of solvents were the following:

	R^Y	Starting Intermediate	MH^+	T_{RET} (min)
Example 68		Intermediate 66	398	2.34
Example 69		Intermediate 67	386	2.29
Example 70		Intermediate 68	412	2.03
Example 71		Intermediate 69	411	2.92
Example 72		Intermediate 70	397	2.67
Example 73		Intermediate 71	385	2.65
Example 74		Intermediate 72	416	2.59
Example 75		Intermediate 73	383	3.22
Example 76		Intermediate 74	400	2.38
Example 77		Intermediate 75	413	2.79
Example 78		Intermediate 76	383	3.22
Example 79		Intermediate 77	396	2.88
Example 80		Intermediate 78	395	2.91

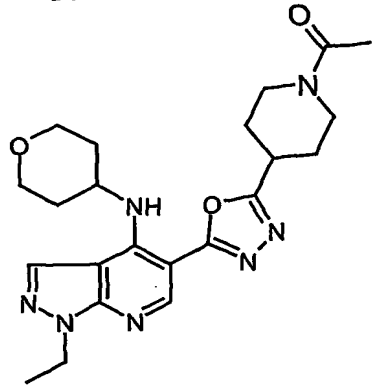
Example 77: 1-Ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-5-[5-(tetrahydro-2*H*-pyran-4-ylmethyl)-1,3,4-oxadiazol-2-yl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine



Alternative Procedure:

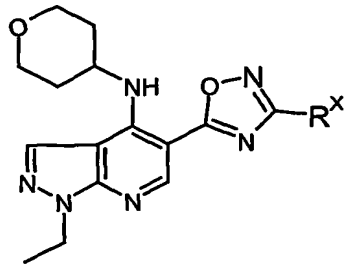
Burgess Reagent (0.168g, 0.74mmol) was added to a solution of Intermediate 75 (0.141g, 0.33mmol) in tetrahydrofuran (2ml). The reaction mixture was heated at reflux for 1.5 hours then evaporated. The residue was applied to an SPE cartridge (silica, 10g) and eluted with cyclohexane:ethyl acteate (gradient of 0 to 100% ethyl acetate over 15 minutes at 15ml/min) followed by ethyl acetate then ethyl acetate:methanol (4:1). Appropriate fractions were combined and evaporated to give Example 77 as a white solid (0.099g). LCMS showed $MH^+ = 413$, $T_{RET} = 2.72$min. ^{1}H NMR (400MHz in $CDCl_3$, 27°C, δppm) 9.12 (br m, 1H), 8.72 (s, 1H), 8.01 (s, 1H), 4.52 (q, 2H), 4.245 (m, 1H), 4.08 (m, 2H), 4.00 (m, 2H), 3.67 (m, 2H), 3.44 (m, 2H), 2.91 (m, 2H), 2.20 (m, 3H), 1.93-1.70 (m, 4H), 1.57-1.40 (m, 5H).

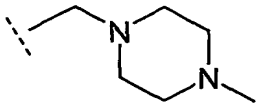
Example 81: 5-[5-(1-Acetyl-4-piperidinyl)-1,3,4-oxadiazol-2-yl]-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



Intermediate 79 (0.18mmol) and Burgess Reagent (0.14g, 0.6mmol) in THF (0.75ml) was heated at 80 °C under an atmosphere of nitrogen for 16 hours. The reaction was concentrated using a stream of nitrogen and the residue dissolved in DCM (8ml). The solution was stirred with water and the phases separated using a hydrophobic frit (Whatman). The organic phase was concentrated in vacuo and the material was purified by mass directed auotprep HPLC to afford Example 81 (0.005g). LCMS showed $MH^+ = 440$; $T_{RET} = 2.52$min.

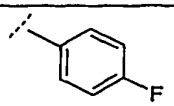
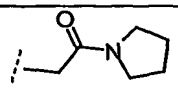
Example 82: 1-Ethyl-5-{3-[(4-methyl-1-piperazinyl)methyl]-1,2,4-oxadiazol-5-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



Example 82, R^X = 

A mixture of Intermediate 16 (0.064g, 0.2mmol), Intermediate 80 (0.172g, 1mmol), a solution of sodium ethoxide in EtOH (0.19ml, 21% solution) and powdered 4Å molecular sieves (0.38g) in EtOH (2ml) were stirred at 82 °C under an atmosphere of nitrogen for 18 hours. The reaction mixture was filtered, the solvent was evaporated in vacuo and the residue was applied to an SPE cartridge (silica, 2g). The cartridge was eluted with (i) cyclohexane, (ii) cyclohexane: ethyl acetate (4:1, 3:2, 1:1, 2:3, 1:4), (iii) EtOAc, (iv) MeOH and (v) 10% aqueous NH_3 solution in MeOH to afford Example 82 as a white solid (0.038g). LCMS showed $MH^+ = 427$; $T_{RET} = 2.10$min.

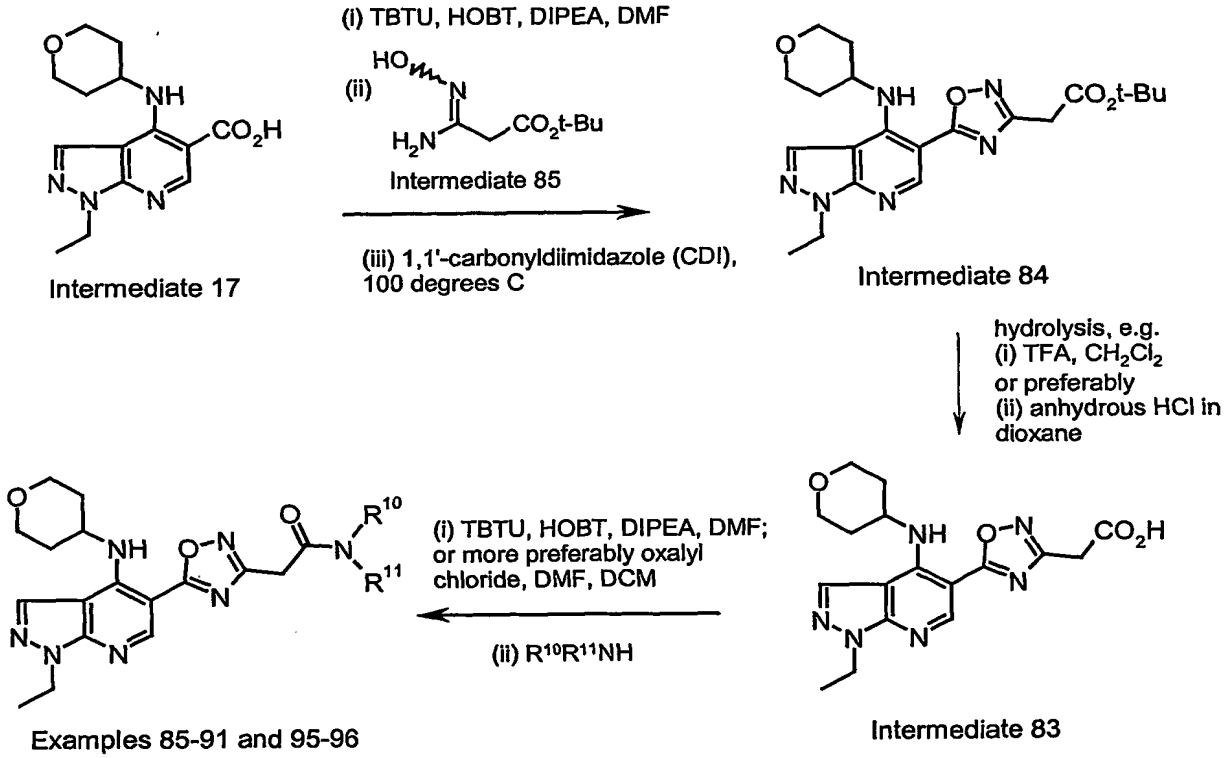
Similarly prepared from Intermediate 16, using the same or similar numbers of moles of reagents and/or volumes of solvents, were the following:

	R^X	Starting Intermediate (instead of Intermediate 80)	MH^+	T_{RET} (min)
Example 83		Intermediate 81	398	2.34
Example 84		Intermediate 82	426	2.6

Examples 85 to 96 – various 5-{3-[substituted]-1,2,4-oxadiazol-5-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amines

Examples 85 to 96 can be prepared from Intermediate 16 using a similar processes to those described for any of Examples 28-31 or 82-84, using a similar or the same number of moles of reagents and/or volumes of solvents.

Alternatively, Examples 85 to 90 and Examples 95 to 96 (all amides) can be prepared from the corresponding carboxylic acid compound Intermediate 83, by activating the carboxylic acid moiety (e.g. using a coupling agent such as EDC, HATU or more preferably TBTU) and reacting the activated carboxylic acid with the appropriate amine $R^{10}R^{11}NH$. This reaction, preferred reagents, and the structure of Intermediate 83 is shown in the following scheme (Intermediate 83 has the same structure as Example 84 but the 1,2,4-oxadiazole side-chain R^X is $-CH_2-C(O)OH$):

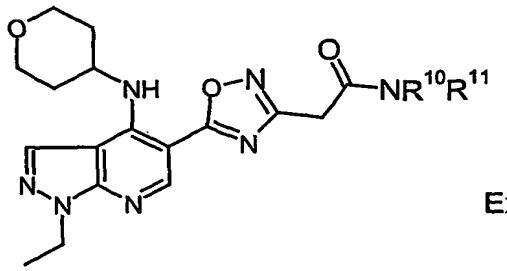


As shown in the scheme above, Intermediate 83 can be prepared by hydrolysis of the corresponding t-butyl ester compound Intermediate 84 (wherein the 1,2,4-oxadiazole side-chain R^X is $-CH_2-C(O)-O-^tBu$). Intermediate 84 can be prepared from Intermediate 17 and Intermediate 85 as shown in the scheme above. The preparation of Intermediate 85 has been shown earlier.

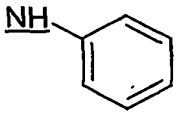
In an alternative embodiment, Examples 85 to 90 and Examples 95 to 96 can be prepared from reaction of carboxylic acid Intermediate 83 with $R^{10}R^{11}NH$ as shown above, but the Intermediate 83 (wherein the 1,2,4-oxadiazole side-chain R^X is $-CH_2-C(O)OH$) might be preparable from Example 84, by hydrolysing the amide bond within R^X in Example 84 to form the carboxylic acid Intermediate 83.

The example numbers and corresponding structures of Examples 85 to 96 are as follows:

Example 85: 2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-phenylacetamide



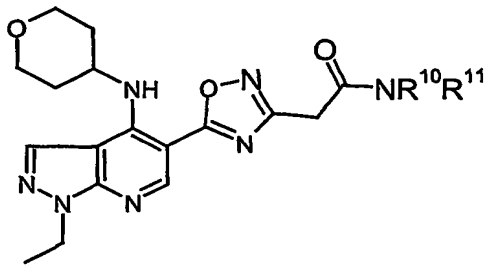
Example 85, $NR^{10}R^{11}$ =

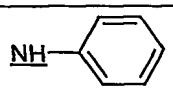
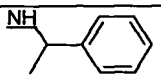
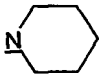
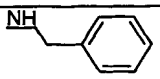
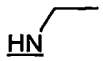


General Procedure for Examples 85 to 90:

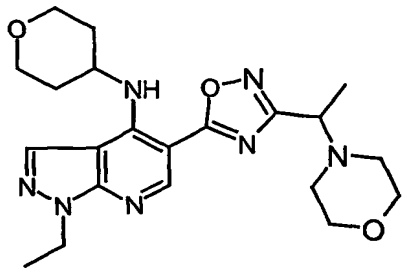
N,N-Dimethylformamide (0.1ml) was added dropwise to a stirred mixture of Intermediate 83 (0.525g, 1.40mmol) and oxalyl chloride (0.18ml, 2.1mmol) in dichloromethane (15ml) at 0 °C under an atmosphere of nitrogen. The resultant mixture was stirred at 0 °C for 1 hour.

An aliquot of the above solution (1.1ml) was added to a solution of the amine $R^{10}R^{11}NH$ (0.6mmol) in dichloromethane (0.5ml). The reaction mixture was allowed to stand at room temperature for 2 hours then applied to an SPE cartridge (aminopropyl, 2g). The cartridge was eluted with chloroform then ethyl acetate / methanol (9:1). Fractions containing the product were concentrated and the residue purified by SPE cartridge (silica, 5g) eluting with dichloromethane, ether, ethyl acetate then ethyl acetate / methanol (9:1). The desired fractions were concentrated to afford the examples given below.



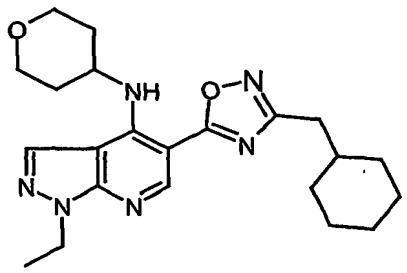
Example Number	$NR^{10}R^{11}$	Source of Starting Amine $R^{10}R^{11}NH$	MH^+	T_{RET} (min)
85		Sigma-Aldrich	448	2.98
86		Sigma-Aldrich	476	2.97
87		Sigma-Aldrich	440	2.81
88		Sigma-Aldrich	461	2.90
89		Sigma-Aldrich	400	2.51
90		Sigma-Aldrich	400	2.51

Example 92: 1-Ethyl-5-{3-[1-(4-morpholinyl)ethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine



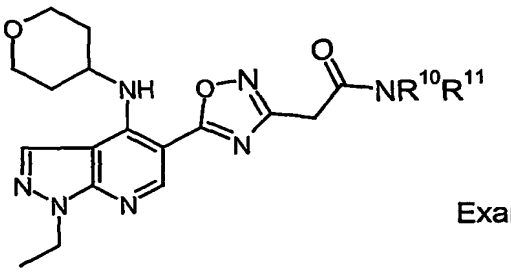
A mixture of Intermediate 16 (0.059g, 0.2mmol), Intermediate 121 (0.161g, 1.54mmol), a solution of sodium ethoxide in EtOH (0.21ml, 21% solution) and powdered 4Å molecular sieves (0.43g) in EtOH (1.5ml) were stirred at 82 °C under an atmosphere of nitrogen for 18 hours. The reaction mixture was filtered and the residue purified by mass directed autoprep HPLC to afford Example 92 (0.007g). LCMS showed $MH^+ = 428$; $T_{RET} = 2.46$min.

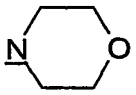
Example 93: 5-[3-(Cyclohexylmethyl)-1,2,4-oxadiazol-5-yl]-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine



A mixture of Intermediate 16 (0.098g, 0.31mmol), Intermediate 122 (0.24g, 0.93mmol), a solution of sodium ethoxide in EtOH (0.21ml, 21% solution) and powdered 4Å molecular sieves (0.43g) in EtOH (1.5ml) were stirred at 82 °C under an atmosphere of nitrogen for 18 hours. The reaction mixture was filtered and the residue purified by mass directed autoprep HPLC to afford Example 93 (0.079g). LCMS showed $MH^+ = 411$; $T_{RET} =$ 3.80min.

Example 95: 1-Ethyl-5-{3-[2-oxo-2-(1-piperidinyl)ethyl]-1,2,4-oxadiazol-5-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine



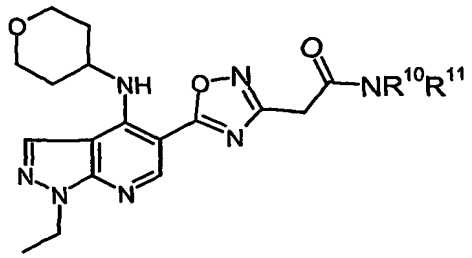
Example 95 $NR^{10}R^{11}$ = 

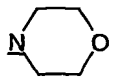
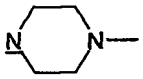
General Procedure for Example 95 to 96:

N,N-Dimethylformamide (0.1ml) was added dropwise to a stirred mixture of Intermediate 83 (0.525g, 1.40mmol) and oxalyl chloride (0.18ml, 2.1mmol) in dichloromethane (15ml) at 0 °C under an atmosphere of nitrogen. The resultant mixture was stirred at 0 °C for 1 hour.

An aliquot of the above solution (1.1ml) was added to a solution of the $R^{10}R^{11}NH$ amine (0.6mmol) in dichloromethane (0.5ml). The reaction mixture was allowed to stand at room temperature for 2 hours then applied to an SPE cartridge (aminopropyl, 2g). The cartridge was eluted with chloroform then ethyl acetate / methanol (9:1). Fractions containing the product were concentrated and the residue purified by SPE cartridge (silica, 5g) eluting with dichloromethane, ether, ethyl acetate then ethyl acetate /

methanol (9:1). The desired fractions were concentrated to afford the examples given below.



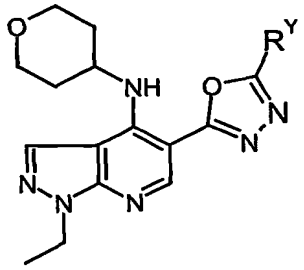
Example Number	$NR^{10}R^{11}$	Source of Starting Amine $R^{10}R^{11}NH$	MH^+	T_{RET} (min)
95		Sigma-Aldrich	442	2.51
96		Sigma-Aldrich	455	2.08

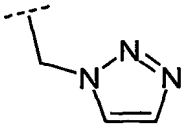
5

Examples 97 to 125 – various 5-{5-[substituted]-1,3,4-oxadiazol-2-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amines

Examples 97 to 125 can be made using processes similar to those described for any of Examples 9, 14, 32-40, 44-45, 60-64, 65-66, and 67-81, using a similar or the same number of moles of reagents and/or volumes of solvents.

Example 97: 1-Ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-5-[5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3,4-oxadiazol-2-yl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine



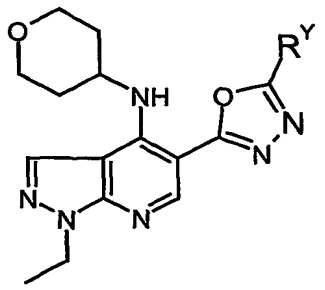
Example 97, R^Y = 

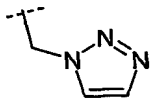
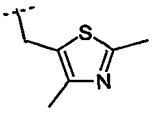
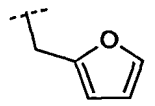
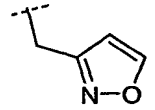
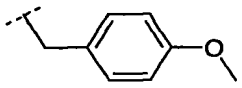
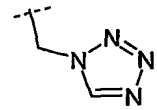
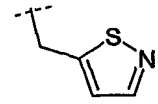
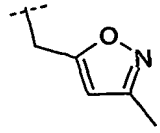
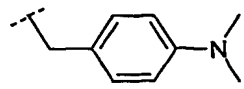
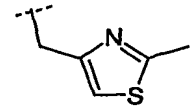
General Procedure for preparation of Examples 97 to 125:

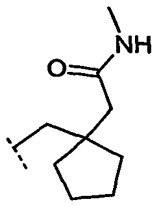
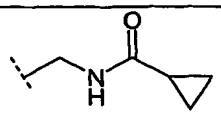
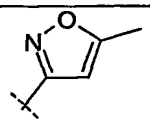
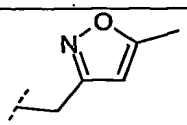
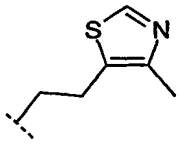
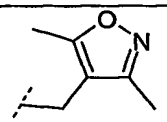
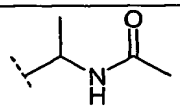
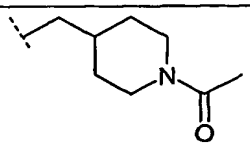
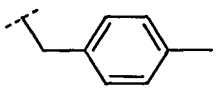
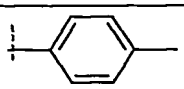
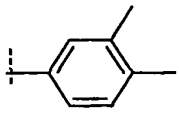
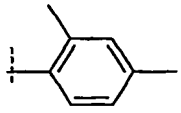
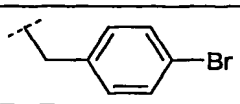
A mixture of diacyl hydrazide Intermediate (one of Intermediates 89-114) and Burgess Reagent (2 equivalents) in N,N-dimethylformamide (1ml) was heated in a microwave for 10 minutes at 120 °C at 150 Watts. The resultant solution was concentrated in vacuo and partitioned between chloroform and water. The organic phase was separated using a hydrophobic frit (Whatman PTFE Filter Media with Polypropylene Housing 5μM pore size) then concentrated. The residue was purified by mass directed auto-prep HPLC.

As either formic acid or trifluoroacetic acid are used in the solvents in the mass directed auto-prep HPLC procedure (see "Machine Methods section hereinbefore), some of the Examples were isolated as the formate salt or trifluoroacetate salt as shown below.

The example numbers and corresponding structures of Examples 97 to 125 are as follows:



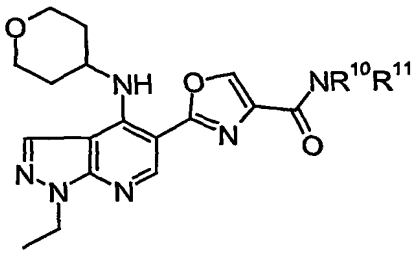
Example Number	R^Y	Diacyl hydrazide Intermediate number	MH^+	T_{RET} (min)
97		89	396	2.47
98 (as formate salt)		90	440	2.79
99 (as formate salt)		91	395	2.97
100 (as formate salt)		92	396	2.69
103 (as trifluoro-acetate salt)		93	435	3.15
104 (as formate salt)		94	397	2.51
105		95	412	2.79
106 (as formate salt)		96	410	2.77
107		97	448	3.01
108 (as formate salt)		98	426	2.76

109 (as trifluoroacetate salt)		99	468	2.85
111		100	412	2.53
112 (as formate salt)		101	396	3.03
113		102	410	2.81
114 (as formate salt)		103	440	2.79
117 (as trifluoro-acetate salt)		106	424	2.80
118		107	400	2.43
119 (as trifluoro-acetate salt)		108	454	2.63
120		109	419	3.20
121		110	405	3.41
122		111	419	3.53
123		112	419	3.65
125		114	3.30	483 / 485

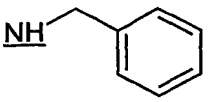
Examples 126 to 147 – various 5-{4-[substituted]-oxazol-2-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amines

Examples 126 to 147 (all amides) can be prepared by reacting Example 57 and the appropriate amine to form the amide bond using a process similar to that described for Example 58, except that HATU is preferably used instead of EDC as coupling agent, and using a similar or the same number of moles of reagents and/or volumes of solvents as in Example 58.

Example 126: 2-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-*N*-(phenylmethyl)-1,3-oxazole-4-carboxamide



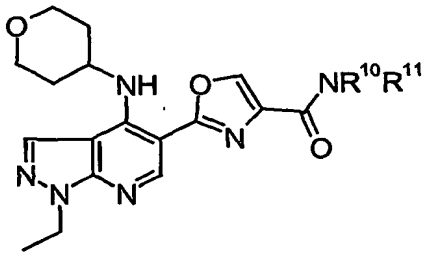
Example 126 $NR^{10}R^{11}$ =

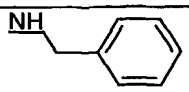
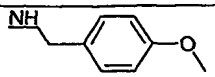
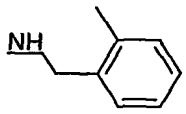
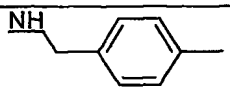
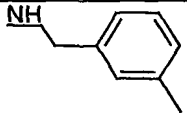
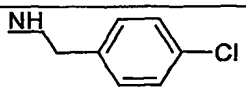
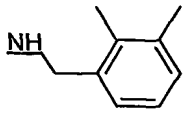
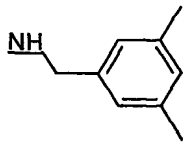
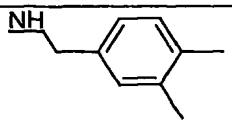
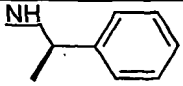
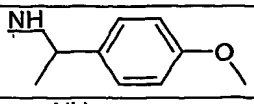
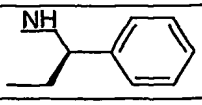


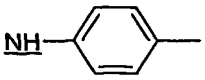
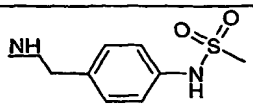
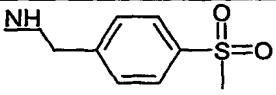
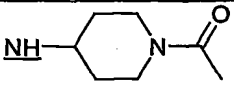
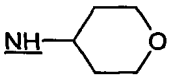
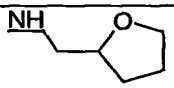
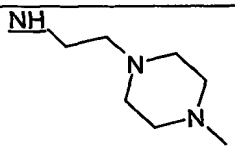
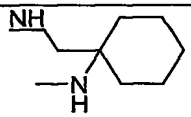
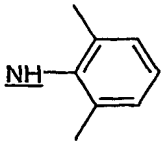
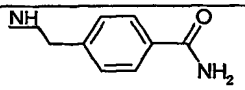
General Procedure for Examples 126 to 147:

A mixture of Example 57 (0.014g, 0.04mmol), diisopropylethylamine (0.0017ml, 0.096mmol) and HATU (0.016g, 0.042mmol) in N,N-dimethylformamide (0.4ml) was allowed to stand for 10 minutes. The resultant solution was added to the appropriate amine $R^{10}R^{11}NH$ (0.05mmol) and mixture agitated by sonication. After standing for 18 hours the solvent was removed in vacuo. The residue was applied to an SPE cartridge (aminopropyl, 0.5g) and the cartridge eluted with chloroform (1.5ml) followed by ethyl acetate : methanol (9:1, 2ml). Appropriate fractions were evaporated in vacuo and the residue purified by mass directed auto-prep HPLC

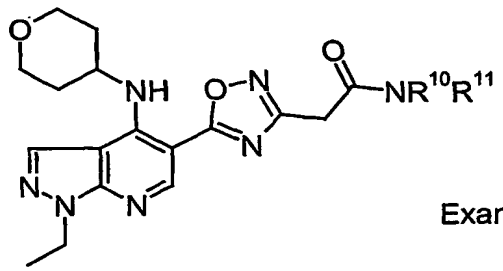
The example numbers and corresponding structures of Examples 126 to 147 are as follows:

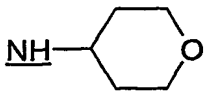


Example Number	$NR^{10}R^{11}$	Source of Starting Amine $R^{10}R^{11}NH$	MH^+	T_{RET} (min)
126		Sigma-Aldrich	447	3.14
127		Sigma-Aldrich	477	3.16
128		Sigma-Aldrich	461	3.26
129		Sigma-Aldrich	461	3.36
130		Sigma-Aldrich	461	3.23
131		Sigma-Aldrich	481	3.35
132		Matrix Scientific or Maybridge	475	3.57
133		Matrix Scientific	475	3.55
134		Matrix Scientific or Pfaulz-Bauer	475	3.46
135		Sigma-Aldrich	461	3.21
136		Pfaulz-Bauer	491	3.22
137		Sigma-Aldrich	475	3.32

138		Sigma-Aldrich	447	3.42
139		J.Med.Chem. 2003, 46(14), 3116	540	2.87
140		WO 02/016318	525	2.86
141		Intermediate 25	482	2.55
142		Intermediate 21	441	2.68
143		Sigma-Aldrich	441	2.89
144		J.Med.Chem. 1999, 42(15), 2870 or Matrix Scientific	483	2.21
145		WO 96/05166	482	3.32
146		Sigma-Aldrich	461	3.23
147		Intermediate 115	490	2.58

Example 148: 2-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)acetamide

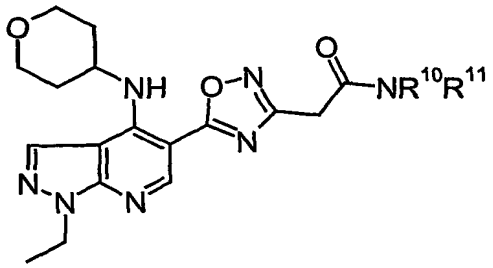


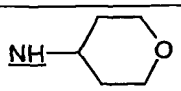
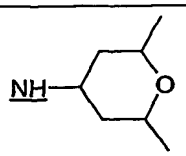
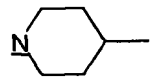
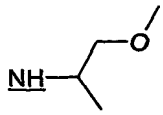
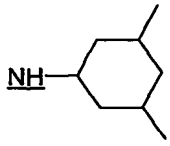
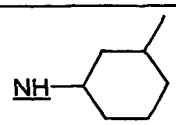
Example 148, $NR^{10}R^{11}$ = 

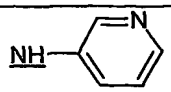
General Procedure for Examples 148-155 and for alternative preparation of Example 84:

N,N-Dimethylformamide (0.1ml) was added dropwise to a stirred mixture of Intermediate 83 and oxalyl chloride (0.18ml, 2.1mmol) in dichloromethane (15ml) at 0 °C under an atmosphere of nitrogen. The resultant mixture was stirred at 0 °C for 1 hour.

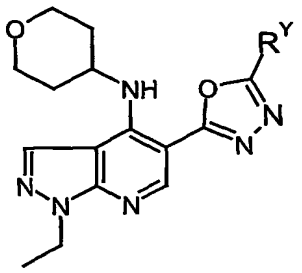
An aliquot of the above solution (1.1ml) was added to a solution of the amine $R^{10}R^{11}NH$ (0.6mmol) in dichloromethane (0.5ml). The reaction mixture was allowed to stand at room temperature for 2 hours then applied to an SPE cartridge (aminopropyl, 2g). The cartridge was eluted with chloroform then ethyl acetate / methanol (9:1). Fractions containing the product were concentrated and the residue purified by SPE cartridge (silica, 5g) eluting with dichloromethane, ether, ethyl acetate then ethyl acetate / methanol (9:1). The desired fractions were concentrated to afford the examples given below.

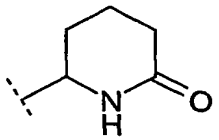


Example Number	$NR^{10}R^{11}$	Source of Amine $R^{10}R^{11}NH$	MH^+	T_{RET} (min)
148		Intermediate 21	456	2.49
149		Sigma-Aldrich (mixture of isomers)	470	2.66, 2.71
150		Sigma-Aldrich	454	2.96
152		Sigma-Aldrich	444	2.57
153		Sigma-Aldrich	468	3.13
154		Sigma-Aldrich	454	2.96

155		Sigma-Aldrich	449	2.51
84 (alternative preparation)		Sigma-Aldrich	426	2.63

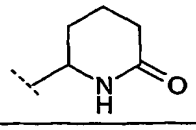
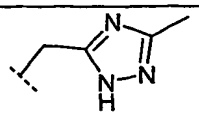
Example 157: 6-{5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,3,4-oxadiazol-2-yl}-2-piperidinone



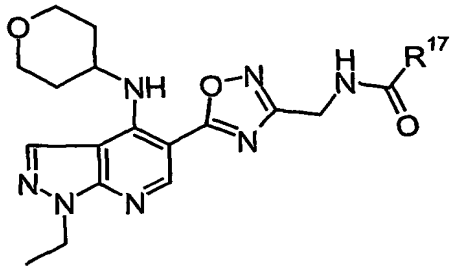
Example 157 R^Y = 

General Procedure for Examples 157 to 158:

A mixture of diacyl hydrazide Intermediate 104 or 105 and Burgess Reagent (2 equivalents) in N,N-dimethylformamide (1ml) was heated in a microwave for 10 minutes at 120 °C at 150 Watts. The resultant solution was concentrated in vacuo and partitioned between chloroform and water. The organic phase was separated using a hydrophobic frit (Whatman PTFE Filter Media with Polypropylene Housing 5μM pore size) then concentrated. The residue was purified by mass directed auto-prep HPLC

Example Number	R^Y	Diacyl hydrazide Intermediate	MH^+	T_{RET} (min)
157		Intermediate 104	411	2.45
158		Intermediate 105	409	2.38

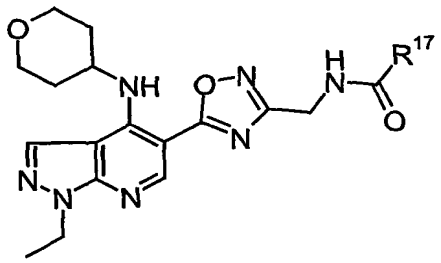
Example 159: *N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)acetamide

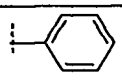
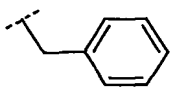
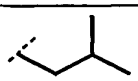


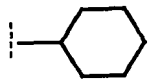
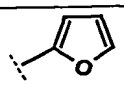
Example 159, R^{17} = Me

General Procedure for Examples 159 to 165:

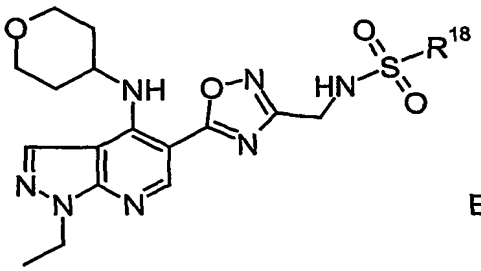
The appropriate carboxylic acid chloride $R^{17}C(O)Cl$ (0.12mmol) was added to a stirred solution of amine Intermediate 118 (0.1mmol) and diisopropylethylamine (0.3mmol) in chloroform (1ml) at room temperature. After stirring at room temperature for 16h, the reaction mixture was applied to a SPE cartridge (aminopropyl, 2g) and the cartridge was eluted sequentially with chlororm, ethyl acetate and methanol. Fractions containing the desired product were combined and blown down under nitrogen. The resulting residue was further purified on a SPE cartidge (silica, 1g) eluting with a gradient of 30-100% ethyl acetate in petroleum ether. Appropriate fractions were combined and the solvents were evaporated to afford the product.



Example Number	R^{17}	Source of Acyl chloride $R^{17}C(O)Cl$	MH^+	T_{RET} (min)
159	CH_3	Sigma-Aldrich	386	2.38
160		Sigma-Aldrich	448	2.82
161		Sigma-Aldrich	462	2.85
162		Sigma-Aldrich	414	2.66
163		Sigma-Aldrich	428	2.79

164		Sigma-Aldrich	454	2.99
165		Lancaster	438	2.68

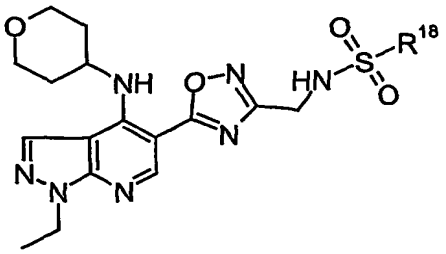
Example 166: *N*-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)methanesulfonamide



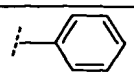
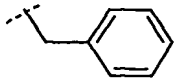
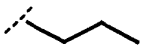
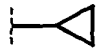
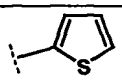
Example 166, R^{18} = Me

General Procedure for Examples 166 to 172:

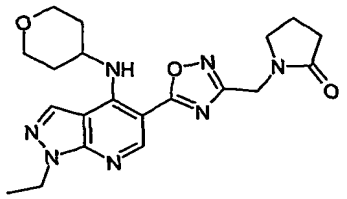
The appropriate sulphonyl chloride $R^{18}S(O)_2Cl$ (0.12mmol) was added to a stirred solution of amine Intermediate 118 (0.1mmol) and pyridine (0.2mmol) in chloroform (1ml) at room temperature. After stirring at room temperature for 16h, the reaction mixture was applied to a SPE cartridge (aminopropyl, 2g,) and the cartridge was eluted sequentially with chlororm, ethyl acetate and methanol. Fractions containing the desired product were combined and blown down under nitrogen. The resulting residue was further purified on a SPE cartidge (silica, 1g) eluting with a gradient of 30-100% ethyl acetate in petroleum ether. Appropriate fractions were combined and the solvents were evaporated to afford the product.



Example Number	R^{18}	Source of Sulphonyl chloride $R^{18}S(O)_2Cl$	MH^+	T_{RET} (min)
166	CH_3	Sigma-Aldrich	422	2.59

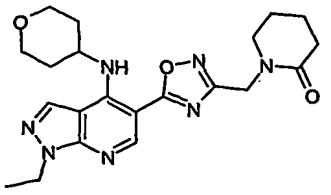
167		Sigma-Aldrich	484	3.00
168		Sigma-Aldrich	498	3.04
169		Sigma-Aldrich	450	2.79
170		Sigma-Aldrich	450	2.83
171		Array Biopharma Inc	448	2.69
172		Avocado	490	2.93

Example 173: 1-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-pyrrolidinone



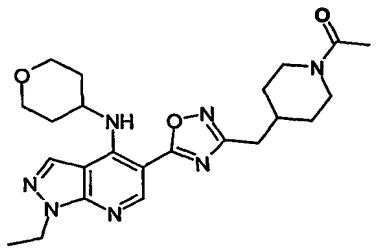
A solution of Intermediate 119 (45mg, 0.1mmol) in dry dimethylformamide (2ml) was added to sodium hydride (60% dispersion in mineral oil, 4.4mg, 0.11mmol), and the resulting mixture was stirred at room temperature. After 16h, the reaction mixture was diluted with water (2ml) and extracted with chloroform (3 x 5ml). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated to give the crude product. Purification of the crude product on a SPE cartridge (silica, 2g) using a gradient of ethyl acetate in petroleum ether afforded Example 173. LCMS showed MH^+ =412, T_{RET} = 2.59min.

Example 174: 1-({5-[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-1,2,4-oxadiazol-3-yl}methyl)-2-piperidinone



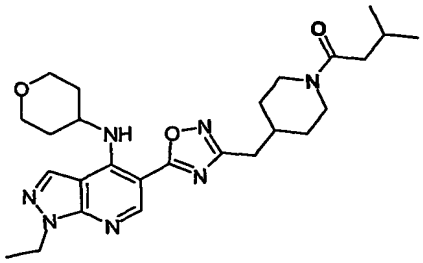
A solution of Intermediate 120 (46mg, 0.1mmol) in dry dimethylformamide (2ml) was added to sodium hydride (60% dispersion in mineral oil, 4.4mg, 0.11mmol), and the resulting mixture was stirred at room temperature. After 16h, the reaction mixture was diluted with water (2ml) and extracted with chloroform (3 x 5ml). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated to give the crude product. Purification of the crude product on a SPE cartridge (silica, 2g) using a gradient of ethyl acetate in petroleum ether afforded Example 174. LCMS showed MH^+ =426, T_{RET} = 2.66min.

Example 175 **5-{3-[(1-Acetyl-4-piperidinyl)methyl]-1,2,4-oxadiazol-5-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



Acetyl chloride (0.04mmol) was added to a stirred solution of Intermediate 125 (0.033mmol) and diisopropylethylamine (0.1mmol) in chloroform (1ml) at room temperature. After stirring at room temperature for 1.5h, a further quantity of acetyl chloride (0.04mmol) and diisopropylethylamine (0.1mmol) were added to the reaction mixture. After 3.5h the reaction mixture was applied to a SPE cartridge (aminopropyl, 1g,) and the cartridge was eluted sequentially with chlororm, ethyl acetate and methanol. Fractions containing the desired product were combined and blown down under nitrogen. The resulting residue was further purified on a SPE cartridge (silica, 1g) eluting with a gradient of 30-100% ethyl acetate in petroleum ether to afford Example 175 LCMS showed MH^+ = 454, T_{RET} = 2.79min.

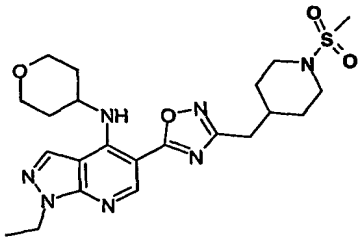
Example 176 **1-Ethyl-5-(3-{[1-(3-methylbutanoyl)-4-piperidinyl]methyl}-1,2,4-oxadiazol-5-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



Isovaleryl chloride (0.04mmol) was added to a stirred solution of Intermediate 125 (0.033mmol) and diisopropylethylamine (0.1mmol) in chloroform (1ml) at room temperature. After stirring at room temperature for 1.5h, the reaction mixture was applied

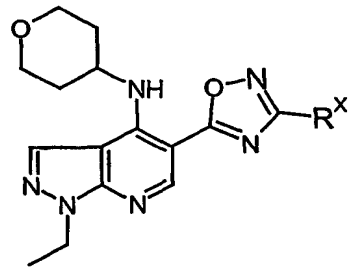
to a SPE cartridge (aminopropyl, 1g,) and the cartridge was eluted sequentially with chloroform, ethyl acetate and methanol. Fractions containing the desired product were combined and blown down under nitrogen. The resulting residue was further purified on a SPE cartridge (silica, 1g) eluting with a gradient of 30-100% ethyl acetate in petroleum ether to afford Example 176. LCMS showed $MH^+ = 496$, $T_{RET} = 3.17$min.

Example 177: 1-Ethyl-5-(3-{[1-(methylsulfonyl)-4-piperidinyl]methyl}-1,2,4-oxadiazol-5-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine

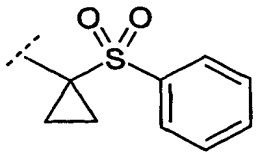


Methanesulphonyl chloride (1.16mmol) was added to a stirred solution of Intermediate 125 (0.033mmol) and pyridine (0.5ml) in chloroform (1ml) at room temperature. After stirring at room temperature for 31h, the reaction mixture was applied to a SPE cartridge (aminopropyl, 5g) and the cartridge was eluted sequentially with chloroform, ethyl acetate and methanol. Fractions containing the desired product were evaporated *in vacuo*. The resulting residue was further purified on a SPE cartridge (silica, 1g) eluting with a gradient of 30-100% ethyl acetate in petroleum ether to afford Example 176. LCMS showed $MH^+ = 490$, $T_{RET} = 2.97$min.

Example 178:

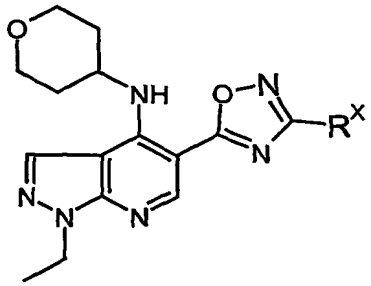


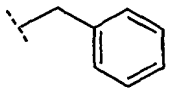
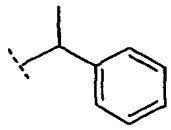
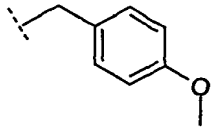
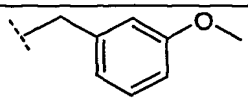
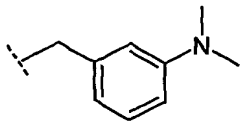
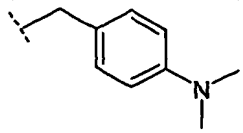
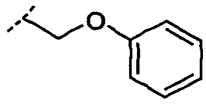
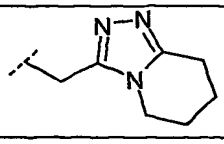
Example 178, R^X =

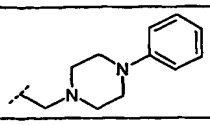


A mixture of Intermediate 16 (0.067g, 0.26mmol), amidoxime Intermediate 126 (0.255g, 1.06mmol), a solution of sodium ethoxide in EtOH (0.87ml, 21% solution) and powdered 4Å molecular sieves (0.68g) in EtOH (2ml) were stirred at 82 °C under an atmosphere of nitrogen for 12 hours. The reaction mixture was filtered and the solvent was evaporated in vacuo. The residue was applied to an SPE cartridge (silica, 5g) and eluted with ethyl acetate: cyclohexane (0 to 70% in 10% increments). Appropriate fractions were combined and evaporated, the residue was purified further by mass directed auto prep HPLC to give Example 178 (0.011g) LCMS showed $MH^+ = 495$; $T_{RET} = 3.2$min.

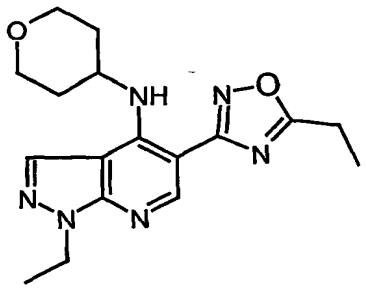
Similarly prepared using the same or similar numbers of moles of reagents and/or volumes of solvents were the following:



Example Number	R^X	Amidoxime Intermediate number (instead of Intermediate 126)	MH^+	T_{RET} (min)
179		127	405	3.35
180		128	419	3.44
181		129	435	3.34
182		130	435	3.35
183		132	448	3.2
184		131	448	3.30
185		133	421	3.35
186		134	450	2.47

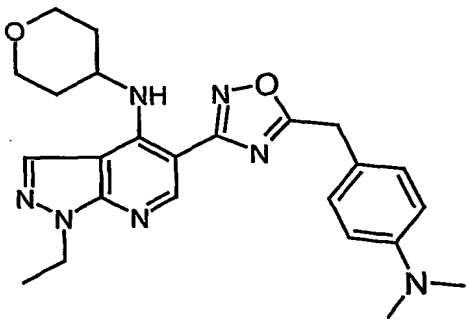
187		135	489	3.01

Example 188: **1-Ethyl-5-(5-ethyl-1,2,4-oxadiazol-3-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



Propionic anhydride (0.015ml, 0.12mmol) was added to Intermediate 138 (0.030g, 0.1mmol) in glacial acetic acid (1.5ml). The reaction mixture was stirred at room temperature for 2 hours then heated at 80 °C for 5 hours. The solvent was concentrated in vacuo and the residue applied to an SPE cartridge (silica, 1g). The cartridge was eluted with cyclohexane then cyclohexane:ethyl acetate (7:3). Appropriate fractions were combined and evaporated to give Example 188 as a white solid (0.015g). LCMS showed $MH^+ = 343$; $T_{RET} = 2.92$min

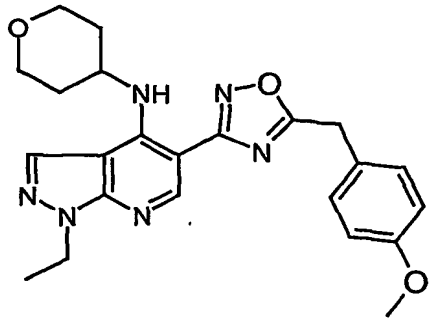
Example 189: **5-(5-{[4-(Dimethylamino)phenyl]methyl}-1,2,4-oxadiazol-3-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



4-(Dimethylamino)phenylacetic acid (0.09g, 0.504mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.097g, 0.51mmol) in dichloromethane (1ml) were stirred at room temperature for 3 hours. The reaction mixture was concentrated then Intermediate 138 (0.07g, 0.23mmol) and diglyme (1ml) were added. After stirring at 20 C for 18 hour glacial acetic acid (0.07ml) and additional diglyme (0.5ml) were added and the mixture heated at 60 °C for 2 hours then at 75 °C for 4 hours. The reaction mixture was applied to an SPE cartridge (SCX, 2g) and the cartridge eluted with methanol then 10% ammonia in methanol. The methanolic

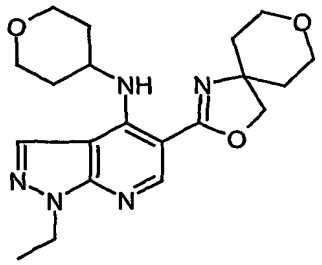
ammonia fractions were evaporated in vacuo and the residue purified by mass directed autoprep HPLC to afford Example 189 as a beige solid (0.004g). LCMS showed MH^+ = 448; T_{RET} = 3.24min.

Example 190: **1-Ethyl-5-(5-{[4-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



Prepared from Intermediate 138 and 4-methoxyphenylacetic acid using a similar process to that described for Example 189 using similar or the same number of moles of reagents and/or volumes of solvents. LCMS showed MH^+ = 435; T_{RET} = 3.26min

Example 191: **5-(3,8-Dioxa-1-azaspiro[4.5]dec-1-en-2-yl)-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine**



Example 191 was prepared from Intermediate 139 using an analogous method to that for Example 49. LCMS showed MH^+ = 386, T_{RET} = 2.71min.